Drug-Eluting Medical Textiles

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Drug-Eluting Medical Textiles: From Fiber Production and Textile Fabrication to Drug Loading and Delivery

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Drug-eluting medical textiles have recently gained great attention to be used in different applications due to their cost effectiveness and unique physical and chemical properties. Using various fiber production and textile fabrication technologies, fibrous constructs with the required properties for the target drug delivery systems can be designed and fabricated. This review summarizes the current advances in the fabrication of drug-eluting medical textiles. Different fiber production methods such as melt-, wet-, and electro-spinning, and textile fabrication techniques such as knitting and weaving are explained. Moreover, various loading processes of bioactive agents to obtain drug-loaded fibrous structures with required physicochemical and morphological properties, drug delivery mechanisms, and drug release kinetics are discussed. Finally, the current applications of drug-eluting fibrous systems in wound care, tissue engineering, and transdermal drug delivery are highlighted.

1. Introduction

The market of medical textiles has great potential as it was worth USD 13.94 billion in 2014, which constituted 10% of the technical textile market in Europe and was predicted to increase its share to about 12% in the near future.[1,2] Various textile features such as their flexibility, light-weight, wide range of dimensions, surface, physical, and structural properties made these constructs favorable to be used in different medical applications.[3,4] Textile fabrics have been extensively used as drug delivery systems in wound dressings, synthetic skin graft substitutes, scaffolds for tissue repair and regeneration, and other topical applications.[4,5]

Textile fibers are categorized into natural and man-made groups based on their origin or the way they have been produced. Natural fibers refer to naturally occurring fibers found in animals, vegetables, and minerals in which their properties depend on the source, the region where they have been produced or stored.[6,7] On the other hand, man-made textile fibers do not occur in nature although they might be made from natural materials in which the physical and chemical properties of the initial material have been altered notably during processing. Man-made fibers can be made from synthetic and natural materials.[7,8] These fibers can be manufactured using different fiber production methods, such as melt spinning,[9] wet spinning,[10] and electrospinning[11] depending on the material used and the properties required for the final fibrous construct.

The cross-sectional shape of the fibers has a significant influence on their physical and mechanical properties, such as flexural rigidity, crispness, and stiffness.[12] Various shapes have been observed in natural fibers. For example, silk fibers have a triangular shape with rounded edges, while wool fibers have oval to round cross-sectional shapes.[13,14] Man-made fibers resulting from different production methods can also have different cross-sectional forms such as round, trilobal, and crenulated, and various morphologies, such as hollow and porous.[5,15,16] In addition, different types of polymers can be combined to produce fibers with the properties required for different medical applications. For example, synthetic and natural polymers can be combined as the natural polymer can provide biological recognition and the synthetic polymer can be used for tuning the mechanical properties.[17] This combination can also appear in various morphologies, including core–shell structures,[18,19] micro/nanotubes, interpenetrating phase morphologies,[20] and nanoscale geometries, such as spheres, rods, micelles, lamellae, vesicle tubules, and cylinders.[21] Finally, produced fibers can be assembled into a 3D construct as woven, knitted, braided, or nonwoven.

In woven textiles, the fibers are intermeshed together through a pattern called "warp" and "weft," which typically results in a

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more robust and dimensionally stable structure than nonwoven structures.[22] However, in nonwoven textiles, no interwoven strands exist and fibers are bound by applying heat, chemicals, pressure, or a combination of these methods. The mechanical and thermal properties can be tuned by orienting fibers randomly or favorably in specific directions;[5,23,24] therefore, suitable constructs for various biomedical applications, such as wound care,[25] and skin grafts,[26] can be obtained. Finally, both woven and nonwoven constructs can be functionalized with different bioactive agents using different drug loading methods.[27]

Fibers can be loaded with bioactive agents or drugs using suitable physical or chemical processes. Examples of physical drug loading methods are absorption or adsorption, coating, and encapsulation, and examples of chemical loading methods are covalent conjugation and grafting.[4,28–31] Fibrous textiles used for drug delivery can also be categorized based on the mechanism by which the drug is released.[32] Some major types of releasing mechanisms are drug or solvent diffusion-controlled systems,[33,34] chemically controlled systems, such as enzymatic or hydrolytic degradation,[35] and externally regulated systems in which the application of an external stimulus, such as ultrasound or electrical field, triggers the release of the drug.[36,37] The release mechanism of the drug-containing fibers as a drug delivery system can be engineered based on the final application to avoid unwanted results, such as burst effect.

To investigate the kinetics of drug release, various statistical methods, such as repeated measures design,[38,39] and model-dependent approaches, such as zero-order model,[40,41] have been developed based on the different phenomena which control the drug release profiles.[42] Among various kinetic models, the zero-order is commonly used as it provides a consistent delivery pace of the drug independent of the concentration.[40] Another simple and frequently used model of drug release kinetic is the Korsmeyer-Peppas Model, the so-called power law, which describes the fractional amount of the drug released over time based on the assumption that the drug diffuses through the polymer or the solvent diffuses inside.[41] Other models take more parameters, such as the effect of desorption, degradation, concentration gradient, and porosity, into account and thus providing more accurate outcomes.[11,43,44]

Developing pioneering biomaterials with tunable physical and chemical properties that are qualified to provide controlled delivery of different biomolecules has great importance in the field of biomedical engineering. In this review, the materials, production, and fabrication of drug-eluting fibers, mechanisms of drug loading and delivery systems, and ultimately different biomedical applications of drug-eluting textiles are discussed. Finally, the benefits and drawbacks of different types of drug-eluting textiles and mechanisms of drug loading and release kinetics are summarized and potential future directions are provided.

2. Classification of Fibers and Materials

The main structural elements in textile products are made from natural and manufactured fibers. Natural fibers are sorted depending on their resource, originating from plants, animals, or minerals.[4] The most frequently used natural fibers in medical products are cotton, silk, and flax.[45,46] In addition, manufactured or man-made fibers can be divided into organic and inorganic fibers. Organic fibers can be further categorized into two large groups based on their sources which can be either natural or synthetic polymers.[5,14,47] Textile fibers classification, including some examples from each group, is shown in **Figure 1**.

2.1. Materials

By considering the difference in intrinsic functionality and physiochemical properties of various materials, selection of the right material or polymer plays a crucial role in designing and developing eluting drug textile. Natural, synthetic polymers, and inorganic compounds can be spun into fibers and form drug-eluting textile for versatile biomedical applications with varying properties, including macromolecule–drug interaction, drug loading efficiency, and release profiles.[48]

2.1.1. Natural Polymers

Natural polymers are widely present and produced in living organisms and are used in numerous fields such as tissue engineering,[49,50] the food industry,[51,52] and the pharmaceutical industry.[53,54] Natural polymers are biodegradable, biocompatible, low/nontoxic, relatively inexpensive, and readily available in many parts of the world.[55,56] However, they have some drawbacks, such as batch-to-batch variations, an uncontrolled hydration rate, and a slow production rate.[56,57] Natural polymers are obtained directly from living organisms, such as carbohydrates and proteins, and those made from renewable resources that need to be polymerized, such as lactic acid and triglycerides.[58,59]

Carbohydrate polymers or polysaccharides are polymerized out of monosaccharides. Polysaccharides have a high molecular weight and can possess different charges or pH values. Various 3D structure of these macromolecules is governed by the linkage configuration of monomers.[60,61] The most well-known carbohydrate polymer is cellulose, which is typically obtained from processed cotton, wood pulp, or bacterial sources.[62] Cellulose and its derivatives are utilized for applications such as wound dressings due to their high tendency to form blood clots.[63,64] Furthermore, fibers obtained from modified polysaccharides such as alginates from algae, chitosan from crustacean shells, hyaluronan from the extracellular matrix (ECM), dextran, and reticulated cellulose from bacterial fermentation are used for biomedical applications. Examples of polysaccharide-based products are wound dressings from alginate or bacterial cellulose,[65,66] surgical sutures made out of cellulose, alginate or chitosan,[67,68] scaffold materials or implants from chitosan, cellulose, or hyaluronan.[69,70]

Protein-based fibers have been commercially produced since the 1950s.[71] Protein-based fibers are widely used in medical textiles to possess biological recognition for cells to adhere to and promote cell infiltration and proliferation compared to carbohydrates and synthetic polymers.[5,72] Protein-based fibers are obtained from living organisms using two main methods. In the first method, proteins are dissolved by solvents or enzymes before being precipitated and reconstituted into fibrils. In the second approach, other elements of living organisms are removed by solvent or enzymes.[73] Natural proteins such as collagen, gelatin from thermal denaturation or acid/alkali degradation of collagen,

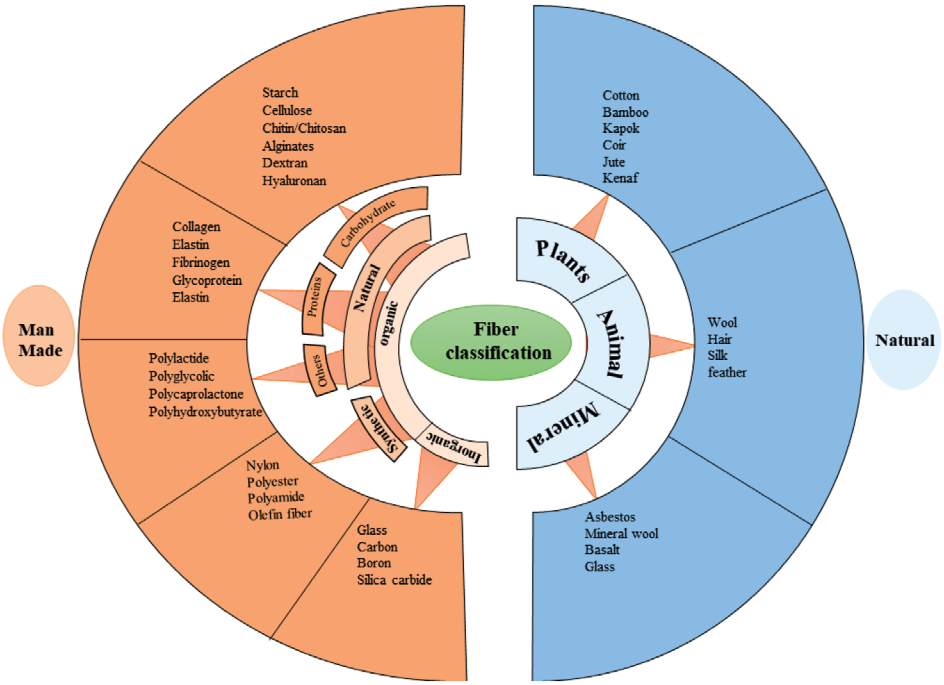

Figure 1. Classification of textile fibers and materials. Fibers are divided into two main categories of natural and man-made fibers, each of which has several subgroups as shown in the figure.

fibrinogen, glycoprotein, and elastin have been extensively used to produce medical textiles.[55,58,74,75]

Natural polymers can be modified via their functional groups, such as amino carboxylic and hydroxyl groups, to improve their functionality, such as solubility, using chemical[51] or enzymatic modifications.[52] For example, chitosan, the deacetylated form of chitin, is a water-soluble polymer at a low pH, while chitin is insoluble in typical regular solvents such as water, organic solvents, mild acidic or basic solution.[76] Fibers spun from some natural polymers lose their mechanical properties in the human body typically faster than required. Thus, hybrid materials are preferred when using natural-based polymers, especially proteins, to reach the desired physical properties and improve the processability.[5,77–80]

2.1.2. Synthetic Polymers

Synthetic fibers are typically produced from chemicals or petrochemicals based materials. Through various polymerization processes, long molecular chains can be formed with different molecular weights and functional groups.[81] Therefore, engineering the structural characteristics of the material, such as melting point, crystallinity, and the glass transition temperature, can lead to medical textiles' advancement and innovation. Three class of widely used synthetic fibers which dominate the market are nylon, polyester, and acrylic.[82] Other popular synthetic polymers such as poly lactic-*co*-glycolic acid (PLGA), polycaprolactone (PCL),[83] polyethylene oxide (PEO),[84] and water-soluble polymers, such as polyvinyl alcohol (PVA),[85] poly(*N*-vinylpyrrolidone) (PVP),[86] are used to fabricate drug-eluting textiles for versatile biomedical applications. There are some challenges with biocompatibility and biodegradability of synthetic fibers, however, they are more preferred than inorganic materials due to carbon element-based nature, which is more similar to the structure of biological tissue.[87]

2.1.3. Inorganic Materials

The inorganic fibers are composed mainly of inorganic chemicals, such as alumina, aluminum, carbon, silicon, and boron, which can be shaped into fibers after processing at elevated temperatures.[88] Inorganic fibers usually have high thermal and mechanical resistance. Many inorganic fibers, such as carbon nanotube, hydroxyapatite, and glass, have been successfully used in biomedical applications such as artificial hips,[89] and vascular stents.[88,90] Figure 1 shows a summarized schematic of fiber classification.

3. Classification of Drug-Eluting Textiles

Drug-eluting medical textiles can be divided into three leading categories of filament fibers, woven, and nonwoven fabrics. Such textiles can be degradable or nondegradable based on the nature of the base polymer from which they are made. Among these three categories, nanofiber nonwovens have attracted more attention in recent years and have been extensively developed for various biomedical applications using different polymers. Additionally, individual fibers produced in the form of continuous filaments have been of great interest too. Such fibers may contain the active bio-agents inside or chemically bond to their surface. Braided surgical suture for wound closure is an example of mono

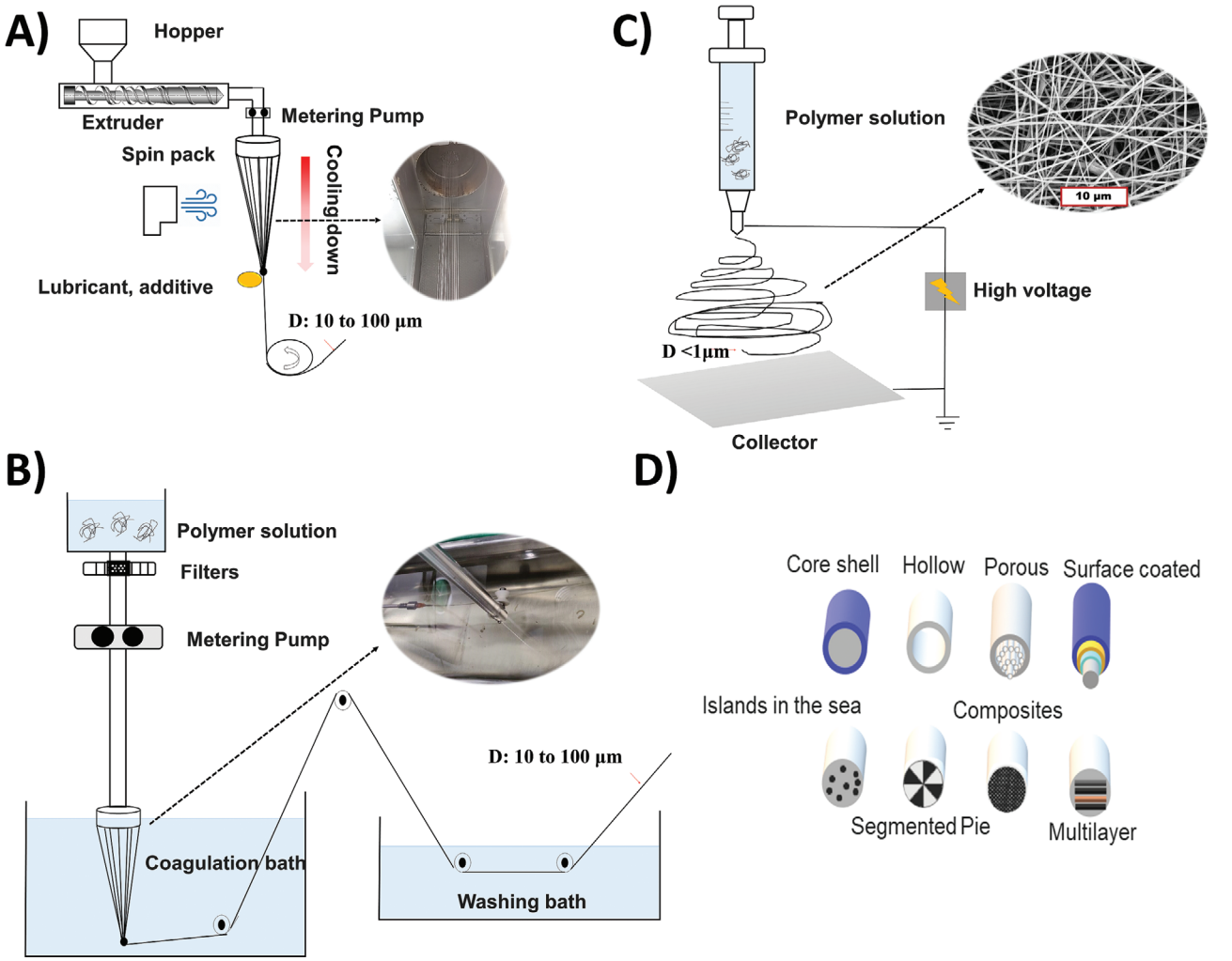

Figure 2. The schematic of fiber production techniques and their representative morphologies. A) Melt-spinning method in which the molten polymer is extruded through the spinning head. B) Wet-spinning process showing that the polymer solution is extruded through a spinneret into an anti-solvent to form a solidified fiber. C) Electrospinning in which polymer solution or melt is subjected to an electric field to fabricate micro or nanofibers, and D) some examples of various morphologies of multicomponent fibers.

and multifilament fibers. Such continuous filaments are usually manufactured using two main techniques of melt spinning and wet spinning based on whether the polymer is spun in melt or solution state.[11,91–93]

Typically, natural fibers have diameters ranging from 10 to 100 µm, and manufactured fibers, using melt or wet spinning, could reach a similar diameter range. However, by using the electrospinning method, the size of produced fibers could decrease to the nanometer scale.[5] Nevertheless, electrospinning is considered as a textile manufacturing technique rather than a fiber production method since nonwoven mats are the output products and not single fibers. Ultimately, multicomponent spinning is an approach to combine two or several polymers in the spinning head using the aforementioned techniques which enables us to obtain fibers with a wide range of biological and mechanical properties.[94] Different classes of drug-eluting textiles including various fabrication technologies are discussed in the following section.

3.1. Fiber Production Methods

3.1.1. Melt Spinning

During melt spinning, the polymer granules or resin is heated within an extrusion to reach the melting point. The molten polymer is then extruded through the spinning head, and based on the number of spinneret holes, either mono- or multifilament is obtained (**Figure 2**A).[91] The geometry of the spinneret defines the cross-sectional appearance of the fibers which can be, for instance, round or trilobal hollow.[5,91] Fibers are then cooled and solidified in the air and further post fabrication processes such as drawing, lubricating, twisting, or entangling prior to being winded on a bobbin can be applied on them.[4]

Melt spinning is typically performed using thermoplastic polymers with high degradation temperatures and low melt viscosities. Therefore, it is not possible to use this technique for some natural polymers, such as chitin or chitosan, due to the strong

interchain forces that raises the melting point above the thermal degradation or the thermal sensitivity of the backbone.[95] However, polymers from renewable sources like poly(L-lactic acid) (PLA),[96] poly(ϵ-caprolactone) (PCL),[97] and cellulose derivatives, such as cellulose acetate butyrate,[98] can be spun using this technique. Finally, due to the high processing temperature, melt spinning is typically not suitable for fabricating drug-loaded fibers, especially when the drug is impregnated into the fibers during the spinning process.[99]

3.1.2. Wet/Gel Spinning

In wet spinning, the polymer solution is extruded through a spinneret into an antisolvent in a regeneration bath where the fluid coagulates and regenerates into continuous solid filaments. Afterward, solvent and antisolvent are washed, and fibers are drawn and dried before winding (Figure 2B). Dry-jet wet spinning is similar in principle to wet spinning; however, the only difference is that the polymer solution will be spun through an air gap before reaching the antisolvent regeneration bath, causing higher molecular chain orientation compared to wet spinning.[100,101] Due to the diffusion of the solvent into the antisolvent, the cross-sectional shape of the fibers is often crenulated with multiple grooves.[5,24,102] Cellulose (viscose rayon),[19] chitosan,[24] alginate,[103] and PCL[104] are some examples of natural polymers that have been spun using this method.

The spinneret diameter, air pressure, injection rate, concentration of the polymer, and the type of solvent and anti-solvent have a noteworthy impact on the characteristics of the final fibers.[24,105] For example, wet spun alginate hydrogel wound dressings with different fiber size (≈55–170 µm), Young's modulus (0.026–0.148 MPa), swelling ratio, release efficacy, water vapor transmission rate, and antibacterial activity were manufactured only by changing the spinning parameters such as air pressure (3–6 bar), concentration of alginate and calcium (1.5 to 3 w v^{-1}% alginate; 0.5 to 5 w v^{-1}% calcium), and nozzle diameter (150–200 µm). The control sample (≈60 µm diameter) was spun with the air pressure of 6 bar, needle size of 150 µm, and calcium and alginate concentration of 5 w v^{-1}%, 1.5 w v^{-1}%, respectively. In this study, the lower pressure or lower injection rate and longer manufacturing time formed loosely bound large-diameter fibers (≈160 µm, $E = 0.04$ MPa), as it allowed more time for calcium to crosslink the fiber. The ten-time decrease in the calcium concentration (0.5 w v^{-1}%) led to the fabrication of thicker fibers (80 µm) since the alginate molecules had more time to expand before complete crosslinking occurred.[106]

Furthermore, coaxial wet-spinning fabrication can be utilized to create core–shell fibers as a method to impregnate both hydrophilic and hydrophobic drugs in one structure. For instance, Wade et al. produced coaxial alginate–PCL microfibers, which were loaded with gemcitabine and nab-paclitaxel in the alginate core and PCL shell, respectively in order to treat unresectable pancreatic ductal adenocarcinoma. More than 94% of the gemcitabine was released in the first 10 h in the simulated body fluid (SBF) and phospholipase D, while nab-paclitaxel exhibited a sustained release profile over three weeks with less than 39% of the drug released in PBS.[107]

3.1.3. Electrospinning

The first usage of electrospinning to fabricate microfibers and nanofibers goes back to 1934, where Formhals released his work on artificial threads using the electrostatic procedure.[108] In this method, fibers with diameters ranging from micrometer to nanometer from a polymer solution or melt subjected to an electric field can be fabricated. The electrospinning system is composed of a syringe pump that controls the flow rate of the solution and a high voltage power supply connecting an electrode with a needle-like nozzle to a collector electrode (Figure 2C).[11,109–111]

The final properties of the fibers are influenced by different processing variables such as voltage, nozzle to collector distance, needle diameter, flow rate, spinning ambient, and solution parameters, such as concentration, viscosity, conductivity, surface tension, and solvent volatility. Fiber orientation can be controlled by selecting the proper collector for a specific end application. Rotating drums or parallel plates can be used to produce fiber mats with aligned and unoriented fibers, respectively.[112] For example, for the fabrication of the scaffolds for vascular grafts, it is essential to produce tubular constructs with the fibers predominantly aligned in the circumferential direction mimicking the preferential alignment of the ECM fibers in native blood vessels.[63,113]

The possibility of incorporating hydrophobic and hydrophilic drugs/proteins and metallic nanoparticles within the bulk phase of fibers makes electrospinning an efficient and highly flexible process to produce drug-eluting fibers.[11,114] We reported the loading and controlled release of tetracycline hydrochloride (TC.HCl) from Curdlan nanofibers over a period of 6 h.[115] Curdlan, an extracellular polysaccharide produced by *Alcaligenes faecalis* bacterium, was blended with polyethylene oxide in different ratios. Antimicrobial activity was acquired by loading TC.HCl to the fibrous system. The cross-linked nanofibers showed an initial burst release behavior in the first 2 h due to the release of TC.HCL attached to the surface of poly(ethylene oxide) (PEO) nanofibers. Afterward, a sustained release profile over 6 hours was observed. Several other polymers, such as PLA,[116] gelatin,[117] PCL,[118] and polymers from bacterial sources, such as polyhydroxyalkanoate,[119] poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate),[120] can be used to produce ultrafine fibers using electrospinning.

Moreover, a summary of spinning feed type and parameters as well as the resultant cross-sectional shape of the fibers using three spinning methods of melt spinning, wet spinning, and electrospinning are provided in **Table 1**.

3.1.4. Multicomponent Spinning

Multicomponent spinning technology can provide the opportunity to tune the mechanical and the biological properties of the fibers by, for example, combining a material with desired mechanical properties for the final use with another material possessing proper biological properties. Multicomponent spinning requires combining two or more polymers at the spinning head while the resulted fibers contain all the polymer components in isolated pieces of the cross-section.[94,122] Melt-spinning, wet spinning, and electrospinning can be utilized to form multicomponent fibers.[11,123,124] Moreover, it is possible

Table 1. An overview of spinning methods, processing parameters, and the resultant fiber shape.[13,112,121]

Spinning methods	Feed type	Process parameters		Cross-sectional shape
Melt spinning	Granules, resin, or thermoplastic polymers	- Viscosity - Mw and PDI[a)]	- Geometry of the spinneret - Drawing ratio - Take up speed - Temperature - Humidity	- Round - Squares - Trilobal - Ellipse - Hollow
Wet spinning	Polymer solution	- Concentration - Viscosity - Mw and PDI	- Geometry of the spinneret - Air pressure - Injection rate - Anti-solvent - Washing - Drying - Drawing ratio - Take up speed - Temperature - Humidity	- Round - Regular serrated - Trilobal - Hollow
Electrospinning	Polymer solution or melt	- Concentration - Viscosity - Conductivity - Surface tension - Solvent volatility - Mw and PDI	- Flow rate - Needle diameter - Applied voltage - Tip to collector distance - Collector types - Temperature - Humidity	- Round
Multicomponent spinning	Polymer solution or melt	- Concentration - Viscosity - Ratio of components - Components miscibility - Mw and PDI	- Similar to melt or wet spinning	- Segmented Pie - Islands in Sea

[a)] Mw (weight average molecular weight), PDI (polymer dispersity index).

to fabricate ultrafine fibers by multicomponent fiber spinning, using thermal treatments or dissolutions to remove the polymer matrix of some of the components of the fibers.[5,122,125]

Bicomponent spinning is used to produce nanofibers via two essential techniques: i) spinning islands-in-the sea (INS), which contains a large number of islands surrounded by the sea (matrix) polymer, and ii) splittable bicomponent fibers, known as segmented pie fibers, which is another approach to produce nanofibers with noncircular cross-section.[122,124,126] Furthermore, bicomponent fiber spinning can be used to spin a resorbable polymer sheath around a nondegradable polymer; drugs and bioactive agents can be loaded into the outer resorbable sheath and released at controlled rates based on the polymer thickness, molecular weight, and morphology.[127,128]

Multicomponent fibers containing bioactive agents or function-regulating biomolecules, such as DNA and growth factors, are widely used in biomedical textiles.[5,123,129] They offer various fiber morphologies, such as core-sheath,[18] side-by-side fibers,[130] micro/nanotubes, and interpenetrating phase morphologies[20] as shown in (Figure 2D). In addition, a large group of nanoscale morphologies[21] such as spheres, rods, micelles, lamellae, vesicle tubules, and cylinders are fabricated by self-assembly of block copolymers.[123,131] Therefore, multicomponent spun fibers have great potential to be designed and fabricated as drug-eluting fibers.

Each aforementioned fiber spinning methods have advantages and disadvantages for producing drug-eluting textiles. For instance, melt and wet spinning methods typically lead to fibers with larger diameters compared to electrospinning; however, an additional fabrication process is usually required to turn fibers into textiles. In addition, melt spinning is considered as a fast solvent-free technique, but the degradation of polymers and incorporated drugs are likely to happen due to the harsh processing conditions such as high temperature and shear rates. Also, extended exposure to organic solvents during the spinning and regeneration might in wet spinning negatively impact the fiber biocompatibility, but it is applicable to many natural-based polymers and benefit from mild temperature processing conditions. Although electrospinning is a simple, inexpensive technique resulting in submicron fibers, the toxicity of the solvents and the instability of the jets, and the processing issues with conductive polymers can be highly challenging.[99,132]

3.2. Textile Fabrication Techniques

Textiles as the final processed products of the fibers are typically categorized to woven or nonwoven fabrics which are reviewed in this section.

3.2.1. Knitted Fabrics

The knitting process creates forming loop stitches in rows (longitudinal direction of fabrics). These stitches intermesh with the next and previous rows and form either flat or tubular fabrics. Unlike weaving, where yarns are always running straight both in

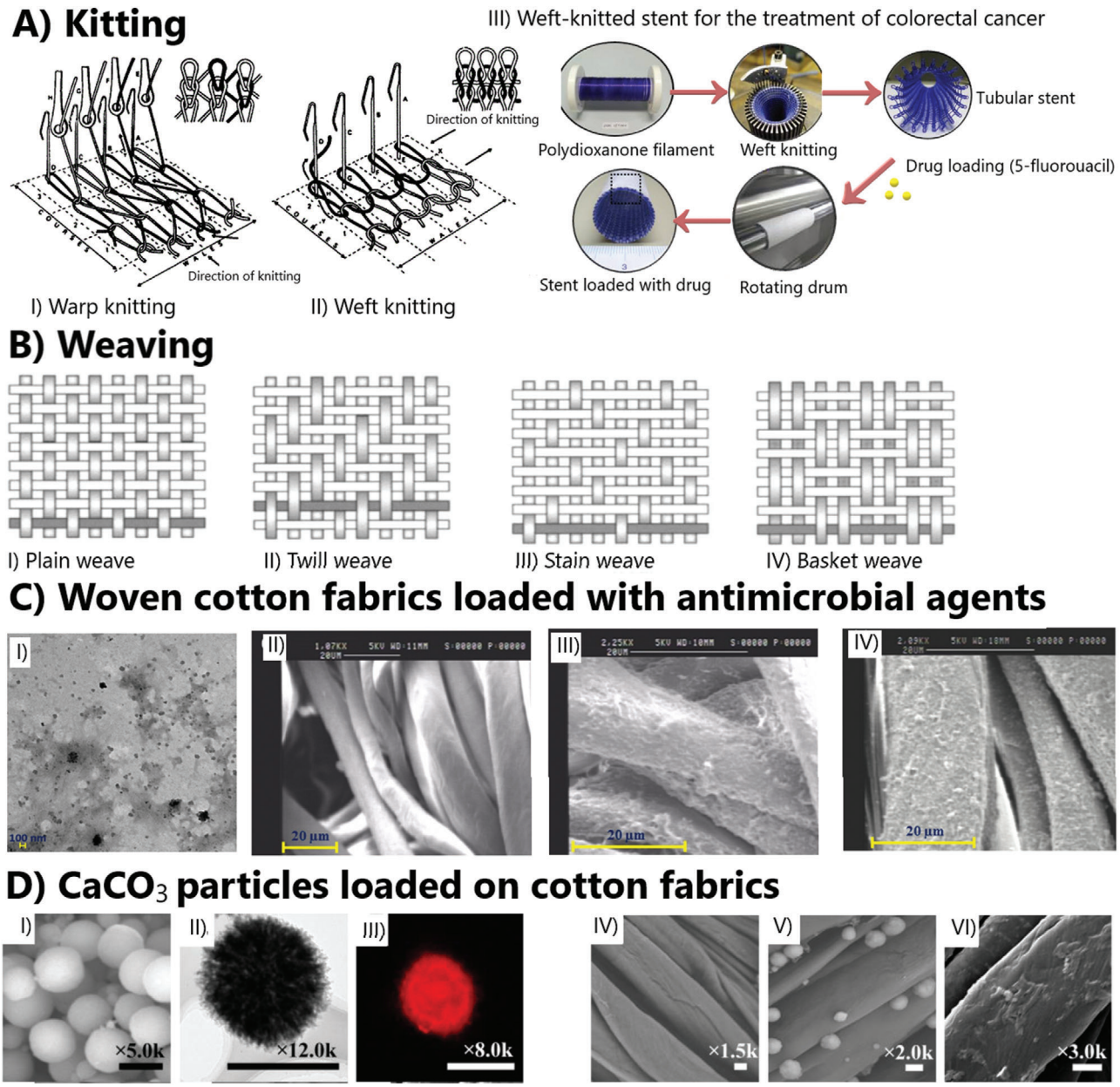

Figure 3. Knitted and woven fabrics in drug delivery applications. A) Schematic drawings of different knitting patterns, (I) warp knitted, (II) weft knitted. Reproduced with permission.[134] Copyright 2000, Elsevier, and (III) weft knitted stent for treatment of colorectal cancer are presented. Reproduced with permission.[136] Copyright 2013, Elsevier. B) Schematic drawings of different woven patterns, plain (I), twill (II), stain (III), basket (IV). Reproduced with permission.[148] Copyright 2000, Elsevier. C) SEM images of chitosan-silver nanoparticles (I), untreated woven cotton (II), and loaded woven cotton fabrics with nanoparticles (III, IV). Reproduced with permission.[144] Copyright 2020, Elsevier. D) SEM images of microgel particles from poly(*N*-vinylcaprolacta65m) and chitosan were prepared in calcium carbonate templates ($CaCO_3$) (I), TEM image of porous $CaCO_3$ (II), CLSM images of microgel after core removal (III), pure cotton fibers (IV), microparticle-loaded cotton (V), and microgel-loaded cotton (VI). Reproduced with permission.[146] Copyright 2017, Elsevier.

the transverse (warp) or the longitudinal (warp) directions, the yarn in knitted fabrics follows the forming sequence of symmetric loops above below the mean path of the yarn. These knitted loops are extensible in the course and wales (*X* and *Y*, respectively) directions, giving the knit fabrics much more elasticity than woven fabrics. Therefore, it is commonly used in medicated bandages and adhesive tapes.[133] Depending on the loops' formation direction, the knitting process is categorized into two main classes of warp and weft knitting (**Figure 3**A-I,II).[134]

More fibers are involved in the knitting process than any other textile technology to allow the fabrication of complex 2D and 3D structures.[135] Li et al. developed a weft-knitted stent for colorectal cancer treatment from 5-fluorouracil (5-FU)-loaded polydioxanone membrane.[136] 5-FU was incorporated into the

nanofibers and coated onto the surface of the knitted stent. The half-maximal inhibitory concentration (IC50) and the median lethal dose (LD50) validated that the membranes outperformed the pure 5-FU and exhibited higher antitumor activity due to the sustainable drug-releasing profile of the coated stent (Figure 3A-III).

Shanmugasundaram et al. developed wound-healing flat-knitted cellulosic fabrics coated with chitosan and alginates.[137] Chloramphenicol and tetracycline hydrochloride drugs were loaded into the coating polymers to improve the antibacterial and wound healing properties. A gel-like with chunky-complexed granules was formed; consequently, heterogeneous films were created upon mixing chitosan and alginates due to the electrostatic interactions between the amino groups in chitosan and the carboxyl groups in alginate. The study concluded that when the drug on the fabric's surface is exhausted, the polymer coating on the surface provides a succeeding shield against bacteria.

In another study, an anti-inflammatory dressing was developed via eluting hydrocortisone (HCr) on activated cotton knitted fabrics for skin-friendly treatment of coetaneous.[138] Drug elution was attained either via covalent grafting of cotton with monochloro triazinyl-beta-cyclodextrin (MCT-β-CD), or through the inclusion of sodium sulfate in an ionic crosslinked chitosan-based hydrogel. The developed systems were deposited on the knitted fabrics and are meant for temporary generation of HCr inclusion. Although the drug-loading method is different, the drug-release mechanism is relatively identical. In the case of MCT-β-CD, the wet conditions, due to perspiration, triggers the substitution of HCr from the internal hydrophobic cavity and promote its transfer to the dermis. For the hydrogel, the medium swells the chitosan-based hydrogel to form a mesh, and then the drug is diffused toward the dermis.

3.2.2. Woven Fabrics

The woven fabric is made by linking two orthogonal arrays of yarns, the first is the warp at 0° and the second is weft at 90°.[139] The yarns are seized in place due to the interyarn friction. The weaving loom technology is well established and provides low manufacturing costs through high productivity rates. The yarns's interlacement acquires stability to the structure and enables complex shape with no gaps. Different woven structures such as plain, twill, stain, and basket weaving are shown in Figure 3B. In some medical applications, woven systems involve the assembly of fabrics that are encapsulated with drugs or active ingredients. Besides woven fabrics can be decorated with bioactive agents via physical absorption and coating or with the aid of modifiers to bond them covalently.[93] Apart from drug-releasing properties, medicated woven fabrics offer defined geometry, pore structure, as well as the strength that suitable for various medical applications such as wound dressing, artificial skin grafts, and scaffolds for tissue engineering.[140,141]

Aykut et al. investigated the weaving of polyvinyl alcohol yarn and cotton to produce a high-strength drug delivery system. The woven fabrics were treated with different concentrations of aqueous crosslinkers, namely borax and glutaraldehyde solutions.[142] In another study, woven cotton and viscose-micromodal fabrics were loaded with caffeine nanoparticles for transdermal antioxidant patches. Once worn next to skin, the system can deliver caffeine for several hours without any further action from the patient.[143] The self-assembled coating on woven cotton fabrics utilizing the layer-by-layer (L-B-L) technique to acquire antimicrobial property was explored by Gadkari et al.[144] In this study, chitosan loaded with silver nanoparticles (Figure 3C-I) was used to coat the surface of the fabrics (Figure 3C-II–IV). The sustained release of silver ions (Ag^+) from cotton fabrics was confirmed by atomic absorption spectroscopy over 48 h.

Bioactive woven cotton gauze is suitable for antimicrobial wound dressings; for instance, medical gauze was decorated with silver nanoparticles and medicated via acacia gum. The woven fabric was found active against the infectious bacterial strains *Staphylococcus aureus* and *Pseudomonas aeruginosa*. [145] Synthetic polyester fabric has been investigated as a carrier for skin lubrication via polytherapeutic substances. The loaded materials increased the durability and abrasion resistance of the textile fabric in addition to its medical effect.[93]

In another study, the microgel particles from poly(*N*-vinylcaprolactam) and chitosan were prepared in calcium carbonate templates ($CaCO_3$) (Figure 3C-I–III) to be on woven cotton fabrics for treatment of sunburn (Figure 3C-IV–VI).[146] The in vitro drug release behavior, in response to temperature, was evaluated at pH 7.4 in phosphate buffer saline. The drug-release profile exhibited extended-release above the lower critical solution temperature due to the shrinkage of the microgels. Mihailiasa et al. reported the mobilization of hyperbranched polymers on the surface of woven cotton fabrics. Nanosponges from hyperbranched β-CD were loaded with melatonin in water/ethanol suspension and mobilized on the surface of the fabrics.[147] A zero-order kinetic behavior was observed for the functionalized fabrics as indication of a typical reservoir diffusion-controlled system.

3.2.3. Nonwoven Fabrics

In general, nonwovens are widely used as medical textiles and are usually considered disposable products. Surgical gowns, masks, surgical drapes, pads, medical filters, and wound dressings can be made from nonwoven fabrics. Its high flexibility, short production cycles, and low-cost production are popular reasons for using nonwovens in medical applications. During the past several years, melt-blowing (**Figure 4**A), solution blowing (Figure 4B), needle-punching (Figure 4C), air laying, wet laying, chemical bonding, thermal bonding, hydro-entangling, spunbonding, and carding have been essential technologies for the formation of nonwovens for medical applications.[149,150]

Most nonwoven fabrics are anisotropic, meaning having more fibers are oriented in longitudinal (machine direction) than the cross direction. The fibers entanglement in a web has a profound effect on the final web properties. Also, fiber configuration impacts fiber packing pore size, capillary dimensions, and capillary orientation. Although nonwovens possess several advantages when used as medicated wound dressing, such as optimal fluid absorbency, breathability, excellent barrier properties, lightweight, and comfort contact with skin, they inherit weak mechanical stability when compared with woven and knitted fabrics. This is mostly attributed to the lack of fiber interlacing and yarn locking.[151]

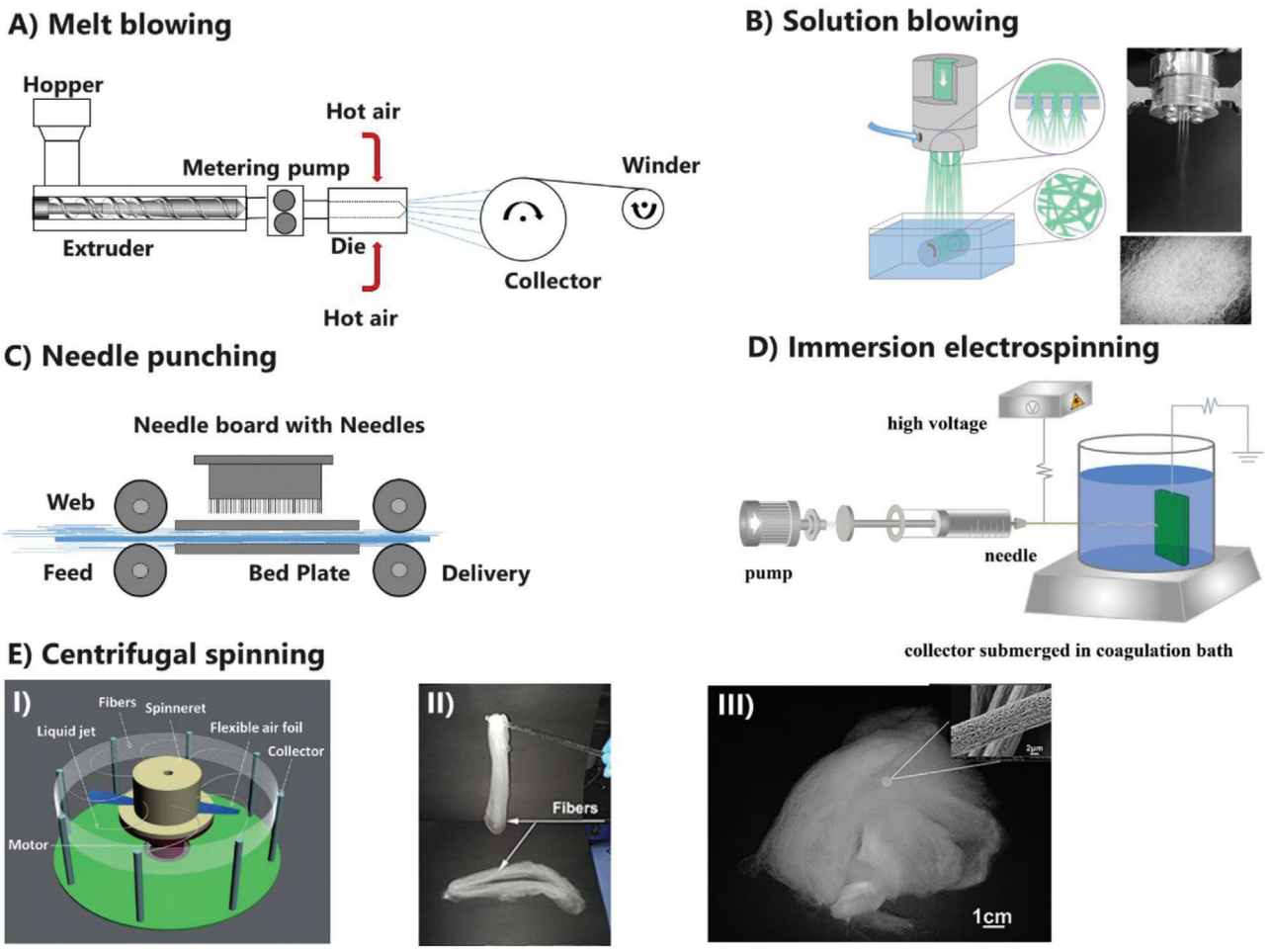

Figure 4. Schematic representation of some nonwoven manufacturing technologies from bulk fibers as well as nanofiber. A) Melt-blowing. B) Solution blowing. Reproduced with permission.[150] Open access, Copyright "Creative Commons CC BY license", 2020, Wiley. C) needle-punching. D) Immersion electrospinning. Reproduced with permission.[153] Copyright 2020, Elsevier. E) Centrifugal spinning (I). Reproduced under the Creative Commons Attribution-NonCommercial 3.0 Unported Licence.[164] Copyright 2017, The Authors, published by the Royal Society of Chemistry, (II) an image of ethylcellulose/polyvinyl pyrrolidone fibers fabricated from centrifugal spinning, (III) SEM images indicating micro- and nano-porous structures produced by centrifugal spinning. Reproduced with permission.[165] Copyright 2017, Elsevier.

The most recent nonwoven innovation is the fabrication of 2D and 3D nanofiber mats for implantable scaffolds, biological filters, and drug-eluting systems. Recent advances in material science enabled the materials and devices to be fabricated in nanoscale. The primary reason for minimizing the object size compartments to nano scales is to provide superior mechanical properties and high surface-to-volume ratio.[152] Electrospinning has been widely investigated to produce nanoscale fibrous structures in various conditions such as immersion electron spinning in which the fiber collectors can be immersed in coagulant solutions (Figure 4D), and the fibers can be collected in the wet state. Different active materials such as drugs can be dispersed in the coagulation bath and loaded to the nanofibers upon its precipitation.[153]

Different techniques are being used for nanofiber formation, among which biocomponent extrusion is widely used. In this technique, two different polymers with various blending ratios are spun together in the same fiber from the same spinneret. Usually, one fiber component can be removed by heat, solvent, or mechanical device, leaving the core fiber alone.[154] Another fiber formation process is the phase separation technique. It is a five-stage procedure in which polymer is dissolved in a proper solvent followed by gelation, solvent extraction, freezing, and freeze-drying. This system relies on phase separation due to physical inconsistency between solvents and polymer. The dissolving agent is extracted and leaving the residual fibers dry.[155] On the other hand, nanofibers from polymer melts can be produced through the melt-blowing technology. Nanofibers can be created by extruding molten polymer into pressurized gas/air streams. Furthermore, self-bonded webs can be collected on a rotating drum or belt. The air jet creates a drag force attunes the fibers rapidly and dramatically reduces its diameter below the nozzle diameter.

Nagy et al. investigated the production of a melt-blown nanofiber system based on a hydrophilic vinylpyrrolidone-vinyl acetate copolymer and PEO plasticizer for drug delivery applications.[156] In addition, the blowing of polymer solutions through concentric nozzles can lead to the formation of nanofibers. Solution blow spinning was first developed in 2009

by Medeiros et al.[157] to fabricate submicron fibers at a high production rate. Nonwovens from PLA as well as PLA/poly(vinyl pyrrolidone) blend containing 20% (wt/wt) antimicrobial Copaibla oil.[158] A recent emerging method for nanofiber formation is centrifugal spinning (Figure 4I).[159] This spinning method relies on centrifugal forces to achieve the high production rate of nanofibers. Both polymer solution and melt can be used to fabricate nanofibers.[160] Stojanovska et al. were the first to report the formation of lignin-based nanofibers via an industrially scalable centrifugal spinning system.[161] The research aimed at the large-scale production of lignin/thermoplastic-polyurethane (TPU) nanofibers for bioactive materials. In another recent study by Rampichova et al., a 3D PCL scaffold was loaded with a combination of TGF-β, IGF, and bFGF growth factors and was used as a delivery system in the treatment of skeletal disorders.[162]

In general, nonwoven and woven drug-loaded fibrous constructs are selected based on the final requirements of the biomedical application. However, drug-eluting woven and knitted fabrics provide more precise geometry, pore structure, and strength than nonwoven fabrics. On the other hand, nonwoven fabrics such as electrospun fibers with smaller pore sizes are more feasible to reach nanostructures with sophisticated morphologies. Nevertheless, considerable challenges must be solved to scale up the fabrication procedure and to transform electrospinning into a commercial and operational process.[99,132] For instance, the poor reproducibility, high dependency of processing conditions on polymer-solution nature, and limitation of the obtainable mesh thickness are the main challenges in aspect of the mass production of nanofiber fabrics.[163]

4. Drug Loading of Fiber-Based Constructs

Drug-eluting systems provide sustained delivery of drugs and other bioactive agents over a period of time from hours to months. Drug-eluting fibers are recently used for delivering different kinds of drugs, such as antibiotics, anti-inflammatory drugs, growth factors, anticancer drugs, proteins, DNA, gens, and vaccines.[166,167] A variety of loading mechanisms are used to produce drug-eluting fibers depending on the parameters such as the type of drug, fiber production method, and the expected drug release profile. For instance, the drug can be incorporated at the prespinning stage by mixing with a polymer solution or after spinning using methods such as coating and supercritical loading.[30,168,169] Coating,[170,171] encapsulation,[172,173] hollow fiber filling,[174] ion exchange,[175–177] inclusion complex,[178,179] direct conjugation,[180,181] hot-melt extrusion,[182] and supercritical impregnation [30,33] are some important methods that have been used to load fibers with drugs through physical adsorption, entrapment, and covalent attachment of the drugs to the fibers.[4]

4.1. Coating

Using this loading method, the drug is incorporated on the surface of the fiber by immersing in a drug solution [171] or by coating with drug encapsulated micro- or nanoparticles[183] (**Figure 5**A). Several coating methods, such as electrochemical deposition,[184,185] immersion,[170] dispersion, and curtain coating[132] are used for drug incorporation onto the fibers. Coating parameters such as pH, solids content, and coating thickness can be tuned to reach the desired coating.[132] In addition, the bioactive components can be grafted to the coating material. Therefore, the coating efficiency is depended on the type of the material, the affinity of the drug to the fiber, coating thickness, and the coating formula.[186]

One of the main issues in the controlled drug delivery systems is the initial burst release. There are some strategies applied to the coating procedure, which can help to achieve sustained release over time, such as using microcapsules and adhesives drugs that can adhere to biological tissues for an extended period of time,[183,187] repeated layers of drug coating on fibers using L-B-L deposition,[188] or taking advantage of processes, such as ultrasound, ion-beam, and irradiation.[4,28,189] For instance, Ma et al.[183] coated cotton fabrics with a solution comprised of tamoxifen drug microencapsulated in gelatin B and acacia gum as an anti-cancer drug for the treatment of breast cancer. Microcapsules remained on fabrics even after 5 and 10 cycles of washing. The coating was stable, and the compound was released over 10 h after an initial bust release. The initial burst effect (30–60%, 1 h incubation time) was attributed to the fact that a significant amount of tamoxifen was loaded in the vicinity of the microcapsule surface.

In addition, different structures of fibers can be formed using coating methods. For example, in a study by Zilberman,[190] core–shell structures were created by coating the core polymers of poly(L-lactic acid) (PLLA) for eluting hydrophilic horseradish peroxidase and nylon for eluting hydrophobic paclitaxel. The shell was made out of drug/protein-containing poly (DL-lactic-co-glycolic acid) to form a porous shell structure. The fibers were dip-coated in fresh emulsions of the shell material and subsequently freeze-dried. The structure and pore size of the shell was tuned by organic:aqueous phase ratio, polymer concentration in the organic phase, and the amount of drug. Both types of loaded drug fibers had an initial burst effect followed by a reduction in the release rate over time, normal for diffusion-controlled systems. In most of the samples, the horseradish peroxidase and loaded PLLA fibers released 90% of the active agent over 90 d. Paclitaxel exhibited a very low initial burst effect (less than 3%), and over 30% of the drug was released within the first 30 days. It was shown that a suitable formulation of the emulsion could lead to a variety of new core-shell structures with favorable drug release profiles.

Coating can also be used to protect the drug layer or as an option for selective contact surface of the fibers with the target area.[132] For instance, dispersion coating in which polymer dispersions are applied and dried on the surface to make a uniform and nonporous film can provide a protective layer for drugs against possibly toxic substances by utilizing separate converting machines or printing press. Also, the desired drug-coated surface area can be obtained by sealing the unwanted sides.[99,132]

4.2. Encapsulation

In this method, incorporation of bioactive agents or drugs can be done either before the fiber production (Figure 5B-I), by homogeneously mixing the polymer and the drug solution,[191] or during

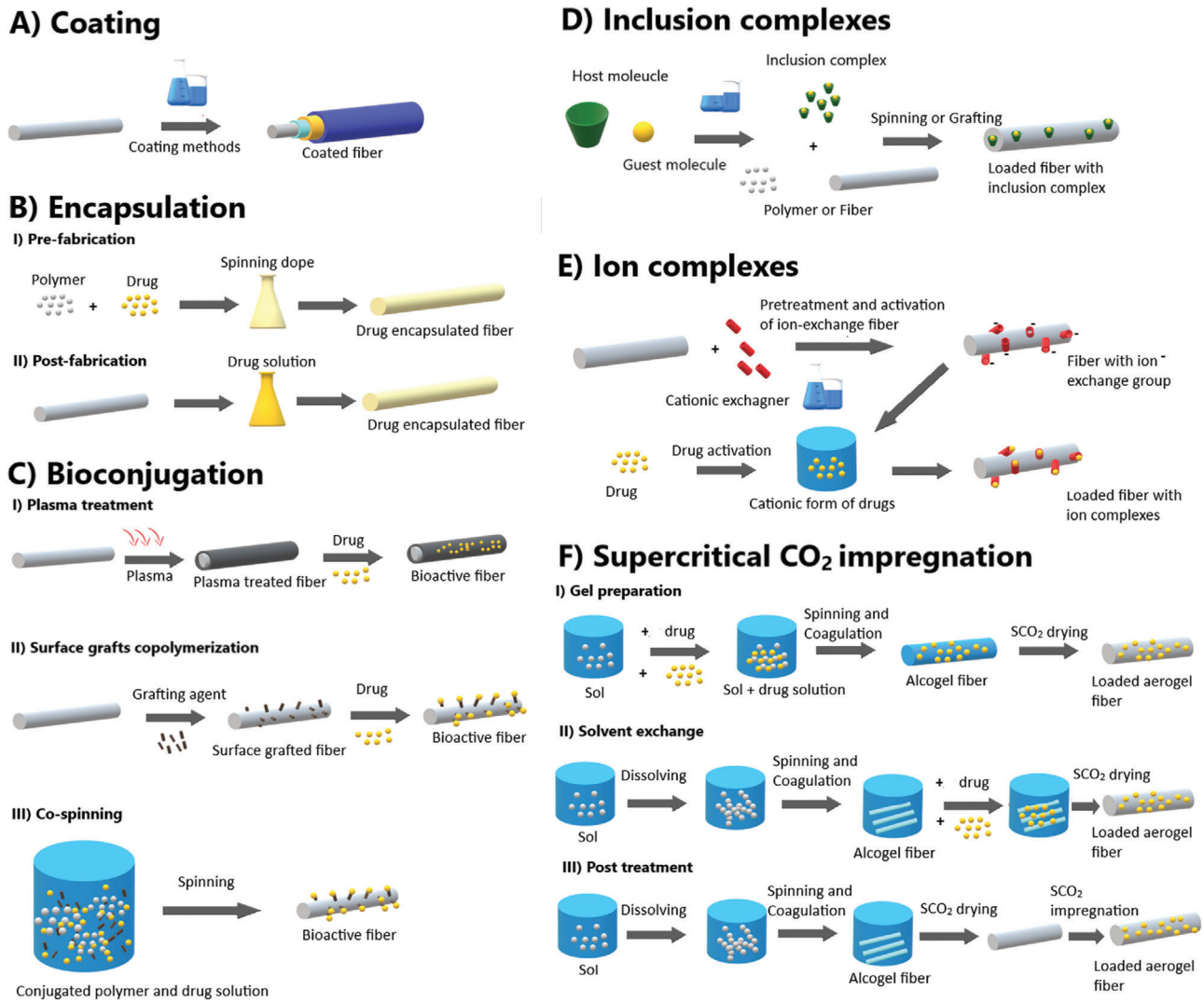

Figure 5. Schematic representation of drug loading methods onto the fiber-based constructs. A) Coating; incorporation of the drug on the surface of the fiber. B) Encapsulation; incorporation of bioactive agents in the fiber matrix. C) Bioconjugation; coupling the bioactive agents to the surface of the fiber in the presence of the functional groups. D) Inclusion complexes; accommodation of a small molecule (the guest, drug) in the cavity (the host, drug carrier), where the complexes can be loaded on the surface of the fiber. E) Ion complexes; binding drugs to the surface of the fibers by using contrasting charges to build ion complexes. F) Supercritical CO_2 impregnation of aerogels; the mild temperature process can be also used to obtain solvent residue-free drug-loaded fibers using CO_2 above its critical coordination (31.1 °C, 73.8 bar).

the post fabrication process (Figure 5B-II), for example, by soaking swellable fabrics in a drug solution.[79,192] Encapsulation of drugs in the fibers is better performed in the preparation stage as a higher dosage of drugs can be loaded.[173] Loading the fibers through the pre-fabrication process depends on the solubility of the drug and the polymer. However, it depends on the swelling of the fiber and diffusion of the drug in the polymer matrix in post fabrication.[4,11] In case of the low solubility of the drug or the polymer in the solution, drug–polymer suspensions can be prepared by dispersing fine drug particles followed by agitation or exposing the drug-polymer solution to ultrasonic waves.[28]

Furthermore, the drug-eluting fiber can be made out of suspension by electrospinning,[193] wet spinning,[194] or microfluidic spinning.[195–197] In wet spinning and microfluidic spinning, encapsulation efficiency dramatically depends on the type of antisolvent used to regenerate and solidify the fibers as it might lead to partial dissolution of the drug.[106,194,195] Wu et al.[198] fabricated microfibers made of polyacrylonitrile (PAN) encapsulated with curcumin and vitamin E acetate. The encapsulation at the solution preparation stage was successful and both drugs were loaded; however, the actual drug loading content was lower than the theoretical drug loading content due to the diffusion of the drugs into the coagulation bath. The drug-loaded filaments showed a microvoid structure caused by entrapment of solvent and non-solvent molecules and subsequent drying of the fibers. The pores could enhance the specific surface area, air permeability, and the drug release rate. Woven textiles from PAN filaments showed good cytocompatibility with prolonged drug release profile over more than 600 h.

4.3. Bioconjugation

In this approach, to couple the bioactive agents to the surface of the fiber, the presence of the functional groups, such as carboxyl,[199] amine,[200] and sulfonic groups,[201] on fibers are required. Surface functionalization can be performed using plasma treatment, wet chemical method, grafting, and co-spinning. When the surface is functionalized, drugs can be coupled to the surface of the fiber by, for instance, chemical conjugation, such as covalent, or physical conjugation, such as adsorption.[180,181,201,202]

4.3.1. Plasma Treatment

In this method, surface adhesion and hydrophobic or hydrophilic properties can be tuned by altering the surface chemical structure. Furthermore, various functional groups, such as carboxyl and amine, depending on the gas used to create plasma, can be added to the surface (Figure 5C-I). Fiber surfaces with activated functional groups created by plasma treatment have been used to couple with protein-based materials, such as gelatin, collagen, laminin, and fibronectin, to enhance cellular adhesion and proliferation.[192,203,204]

4.3.2. Wet Chemical Method

Plasma treatment is limited to the surface area, whereas wet chemical methods, such as partial surface hydrolysis, can be a solution to increase the conjugation sites.[205,206] This means that the surficial ester linkages in the polymer chain backbones of biodegradable aliphatic polyesters under acidic or basic conditions will be chemically cleaved; therefore, carboxylic and hydroxyl groups will be generated while the polymer remains water-insoluble.[180] Sun et al.[207] investigated simple alkali hydrolysis as an efficient way to modify polyesters, such as PCL, to couple a cell-recognizing peptide to a carboxylated surface.

4.3.3. Graft Copolymerization

Another approach to conjugate drug molecules on the fiber surface through chemically or radiation-induced graft polymerization is graft copolymerization (Figure 5C-II).[180,208] Using this method, multifunctional groups, hydrophobic or hydrophilic, can be tailored.[180] In a research done by Park et al.,[209] poly(glycolic acid) (PGA), PLLA, and poly (lactic-co-glycolic acid) (PLGA) electrospun fibers were functionalized using oxygen plasma treatment, and in situ grafting of hydrophilic acrylic acid (AA) to incorporate hydrophilic functional groups resulted in better fibroblast proliferation.

4.3.4. Co-spinning

In this approach, it is essential to achieve a homogenous polymer blend solution of nanofibers, nanoparticles, and functional polymer segments prior to spinning.[4,180] Functional groups can be located on the fiber surface via co-spinning of different polymers containing various functionalities (Figure 5C-III). For example, Sun et al.[210] fabricated antibacterial surface-biofunctionalized electrospun PEO fibers as a host polymer and an oligopeptide conjugate. This was a single-step method to obtain surface biofunctionalized fibers, which possess three repeated units of a triad serine, glutamic acid, and glutamic acid $(Ser\text{-}Glu\text{-}Glu)_3$ using the co-spinning method.

4.4. Inclusion Complexes

An inclusion complex is a compound in which a small molecule (the guest) can be accommodated in its cavity (the host) (Figure 5D). Usually, inclusion complexes are referred to as textile slow-release systems due to their ability to release the guest compound in a slow and continuous manner.[4,132,211] Several large molecules such as CD, fullerene, azacrown ether, and their derivatives can be used to produce inclusion complexes.[212,213] The most well-known inclusion compound used in drug-releasing textiles is CD, cyclic alpha-1,4 linked oligosaccharides consist of numerous D-glucose units, alpha-, beta-, and gamma. The hydrophilic interior and hydrophobic exterior of CDs make them favorable substances in the complexation of drugs.[213–215]

The first step in loading fibers is to introduce cyclodextrin on the surface of fibers which can be achieved by using one of the bioconjugations explained in Section 4.3.[178,179] Then, the surface of the fibers is ready to form inclusion complexes with bioactive agents for drug delivery purposes (Figure 5D).[211] As an example of using CD, wool fibers grafted with β-CD using low-temperature oxygen plasma treatment and dyed with antibacterial natural colorant berberine[178] or polyamide fibers coated with a CD–ciprofloxacin[179] proved to have significant antibacterial activity.

Furthermore, CDs can be introduced into the fiber during fiber fabrication. For example, CDs entrapment within the fibers was achieved by melt spinning using materials such as polyesters and polyamides. It was shown that instant cooling of the fiber exiting from the spinneret forced CDs to migrate to the surface of the fiber and thus made them accessible to form complexes with drugs. This migration occurred due to hydrophilic external surface of the CD which blocked complete perforation into the fiber.[216,217] In another research, Yildiz et al.[218] studied the potential of co-spinning conjugated polymer and drug solution to fabricate self-standing and quick-dissolving fibrous textiles from carvacrol/CD inclusion complexes. The result enhanced the hydrosolubility, thermal stability, and antioxidant activity of the fibrous web, which can have a potential to be used for food and oral care applications.

4.5. Ion Complexes

Drugs can bind to the surface of the fibers by using contrasting charges in order to build ion complexes. Drug release is then relying on the external solution or the ability of the fiber surface to preferentially exchange counter-ions that are influenced by the type and the concentration of the surface ion-exchange groups (Figure 5E).[4,27,99,132] Ion complexes undergo a stoichiometric exchange reaction and can have extensive exchange

potential, making them a suitable candidate as a multiple drug carrier.[35,176,177] In a study by Liao et al.,[175] fibers from a blend of chitosan-alginate with charged surfaces were produced. Drug complexation was created with several bioactive charges including dexamethasone, BSA, growth factor (PDGF-bb), and avidin mixed with either chitosan or alginate solution. Electrostatic interaction among the charged fiber and the charged drugs controlled their release mechanism and profile from the fibers; therefore, the elution time of the components from these fibers ranged from hours to weeks.

In another study, Gao et al.[219] investigated the drug release from the poly(propylene-g-styrene sulphonic acid) fibers loaded with tramadol hydrochloride as a model drug. The tramadol was consistently delivered from the drug-loaded fiber when iontophoretic, a noninvasive technique to increase transdermal penetration using a voltage gradient, was applied since combining ion-exchange fiber with iontophoresis will decrease the fluctuation of the drug release.[220] Some commercially available ion-exchange fibers are the Smopex fibers, which contain polyethylene backbone grafted with other polymers such as polystyrene sulphonic acid (Smopex-101), polyacrylic acid (Smopex-102),[221] or polyamide (Smopex-108).[176] In short, ion-exchange fibers have demonstrated great abilities to release various ionic drugs loaded into ion-exchange groups. These functional fibers can be ultimately used to produce woven or nonwoven fabrics.

4.6. Supercritical CO_2 Impregnation

Supercritical impregnation is a mild temperature process to load fibers with bioactive agents, providing a drug-loaded textile free of any solvent residue. CO_2 above its critical temperature and pressure, 31.1 °C and 73.8 bar, respectively, is in the supercritical state. The critical temperature of CO_2 is relatively low and easily achievable, making it a mild solvent for temperature-sensitive materials. Supercritical CO_2 ($scCO_2$) is a "tunable solvent" as its properties, such as viscosity, density, and diffusivity, can be controlled by varying pressure or temperature.[15,30,222,223] Furthermore, $scCO_2$ has an intermediate behavior between gas and liquid, possessing a density similar to that of the liquid, 0.2–1.5 g cm^{-3}, and transport properties close to those of the gas. In addition, $scCO_2$ is a dissolvable medium for nonpolar low molecular weight compounds; however, in case of poor solubility, a cosolvent like ethanol is used to increase the solubility of the polar molecules.[30,224]

In biomedical applications, temperature and pressure range between 35 and 55 °C and 90–200 bar have been investigated for drug loading.[30,225] This method has been mainly used in producing and loading aerogel. However, due to the low mechanical properties of aerogels in fibers, they have not been extensively investigated.[223,226] Drug loading in the aerogel fibers can be done either during gel preparation (Figure 5F-I), during the conventional sol-gel process, so-called solvent exchange (Figure 5F-II), [227] or during the post treatment of the synthesized gel (Figure 5F-III).[228] Post treatment loading has been extensively utilized for nonaerogel materials too.[225,228] The post treatment loading process consists of three main steps. At first, the solute is dissolved in the $scCO_2$ and then the polymer is exposed to the solution of $scCO_2$, where the bioactive agents and the solution diffuses into the polymer bulk. The loading efficiency is dependent on the CO_2 ability to swell the polymer matrix.

Finally, the last step is depressurization, in which CO_2 and non-impregnated drugs are removed from the loading chamber.[229,230] The drug loading efficiency in this method depends on the solubility of the drug in CO_2, CO_2 sorption, polymer swelling, the affinity of the drugs to the polymer, and the processing factors, such as pressure, temperature, loading time, diffusion process, and depressurization conditions.[30,230–232] Some example of loaded textiles are cellulose acetate (CA) fibers impregnated with menthol and vanillin,[222] chitosan with dexamethasone as a scaffold for bone tissue engineering,[233] and collagen and cellulose as a commercial wound dressing (Promogran) impregnated with anti-inflammatory jucá (*Libidibia ferrea*).[234]

Using the supercritical impregnation method, fibers with different geometries can be loaded using hydrophilic or hydrophobic drugs. For instance, a dual-drug solvent exchange impregnation into core–shell electrospun nanofibers was achieved by $scCO_2$ method.[235] The $scCO_2$ was able to load the model BODIPY 493/503, as a hydrophobic model drug, into the hydrophobic PCL core and impregnation of the rhodamine B, as a hydrophilic model drug, into the hydrophilic shell. Hydrophobic or hydrophilic drug-polymer interactions improved the drug loading and caused a steady linear release. Since $scCO_2$ localized the drugs throughout the entire fiber matrix, $scCO_2$ drug-loaded fibers demonstrated a controlled and extended bimodal release compared to immersed fibers in a solution containing the two drugs. Therefore, $scCO_2$ can be used as a tunable medium for loading various drugs into a fibrous structure.

Selecting a suitable drug impregnation method is crucial in the final properties of the fibrous delivery system. Therefore, several factors should be considered in the selection process including material or production cost, biostability, biodegradability, toxicity, ex vivo or in vivo drug delivery, and their compatibility with the fiber/textile production. For instance, in the case of inclusion complexes, known for creating slow-release systems, modified cyclodextrins costs are high; also their final fixation on the textile surface is required since high dosage release of cyclodextrins can be toxic.[32,48] The fiber spinning condition, final morphology, and drug loading capacity are other factors that can limit the choice of impregnation method. Nevertheless, conventional fiber and drug loading production techniques such as coating and incorporating the drugs into the polymer or melt solution are yet favorable due to their simplicity.

5. Characterization of Drug-Eluting Textiles

Several methods are used to characterize drug-releasing textiles; however, the most common methods are those that determine the chemical functionality, biological activity, surface morphology, mechanical properties, durability and degradation, and drug-loading and release kinetics. Infrared (IR) spectroscopy is widely used in identifying the chemical functionalities of fiber surfaces. Most chemical functionalities absorb infrared frequencies that correspond to their molecular vibrational frequencies. IR can detect the majority of the mobilized compounds on the textile surfaces. In addition, any changes to the surface morphology of the textiles can be detected by scanning electron microscopy

(SEM).[236] The surface analysis can also give an idea about the durability and surface degradation, which indirectly refers to the release behavior of the drug-eluting textiles.[237] For the degradation studies, simulated body fluids at physiological temperature are used. Enzymes can be added to the testing medium to accelerate the degradation of the base textiles.[238]

Determining the biological activities of the medical textiles, especially, antibacterial properties is essential when antibiotics are incorporated. AATCC 100 and 147 are widely used in the antimicrobial assessment of textile fabrics. In addition, evaluation of the physical and mechanical properties of the drug-eluting systems is essential in order to determine their suitability for different applications.[239] Finally, understanding the release behavior of the drugs is crucial to satisfy the requirement of the final application. Different mechanisms of drug release from fiber-based constructs are thoroughly discussed in the following sections.

5.1. Drug Release Mechanisms

Textile-based drug release systems should be able to deliver the drugs efficiently, accurately, and for a defined timeframe. The term "release mechanism" illustrates the procedure in which drugs are transported or released.[132] In textile-based systems, regulation of the drug release rate is dependent on parameters such as geometry (size and shape), morphology, and material properties, such as swelling and degradation, of the carriers or host molecules.[27,99,132]

The most addressed drug release mechanisms are immediate, extended, and triggered or delayed release.[27,132,240] As shown in **Figure 6**A-I, in the immediate release, there is a rapid release of the drugs in a short time. However, in extended release (Figure 6A-II), the drug is delivered at a lower rate constantly or variably over an extended period of time. Finally, in triggered release (Figure 6A-III), different stimuli, such as pH or temperature, initiate the release procedure, which can be immediate or extended.[27,132]

5.1.1. Immediate Release

In some circumstances, where an instant reaction is necessary, immediate drug release is preferred. For example, a rapid release rate of antibiotics in the first hours following the biomaterial implantation is vital to avoid implant-related infection.[241,242] He et al.[243] spun a fibrous structure blend using electrospinning to incorporate a model drug TC.HCl into PLLA fibers. The nanofibers from the TC.HCl /PLLA blend showed an immediate release and prevented bacterial infection. Johnson et al. investigated the release of a hydrophobic model drug, Nile Red, from the emulsion electrospun fibers containing PCL (oil) and nonionic surfactant, Span 80. The samples with and without surfactant exhibited an initial burst release continued by a slower continuous drug release over one hour. However, the burst release of the model drug from nanofibers with surfactant was lower, due to the interaction of the model drug at the interface of emulsion and the fiber body and the lower surface area of samples with the surfactant.[244]

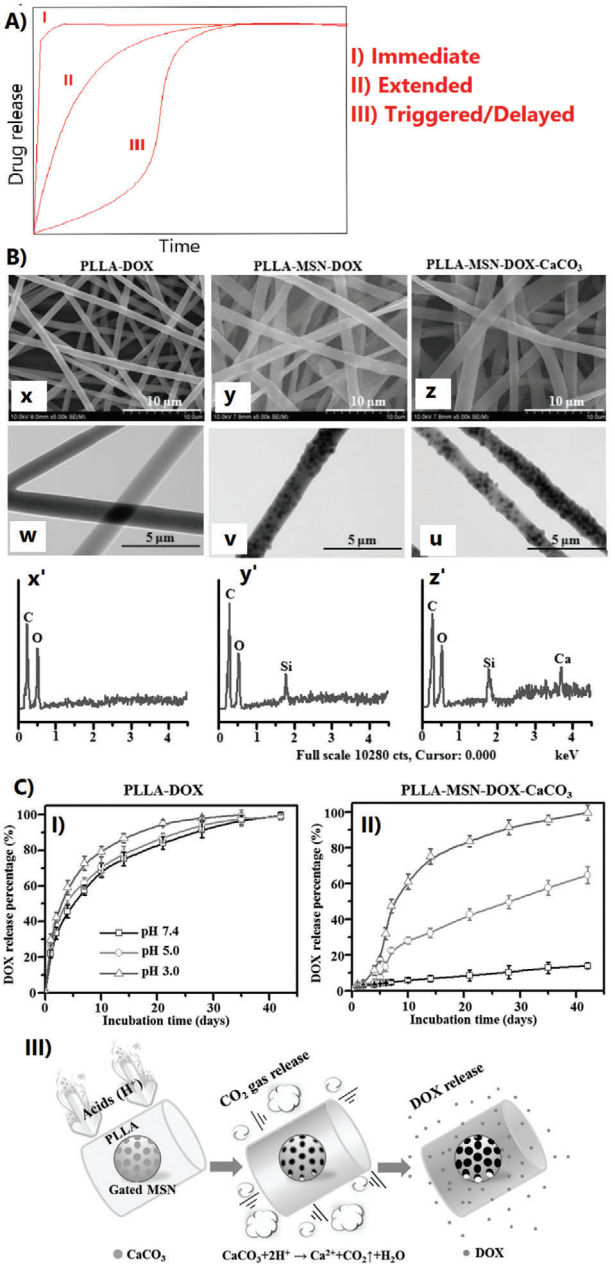

Figure 6. Drug release mechanisms. A) Most common examples of drug release mechanisms, immediate, extended, and triggered or delayed-release. B) SEM (x,y,z) and TEM (w,v,u) images of PLLA fibers co-electrospun with (x,w) DOX, (y,v) MSN-DOX, and (z, u) MSN-DOX-$CaCO_3$. EDX spectra of x') PLLA-DOX, y') PLLA-MSN-DOX, and z') PLLA-MSN-DOX-$CaCO_3$. C) Drug release profiles of I) PLLA and II) PLLA-MSN-DOX-$CaCO_3$ at various pH conditions. III) Schematic explanation of drug release mechanism of electrospun fibers. The interaction of protons (H^+) from the acidic media diffusion into the nanofibers; protons react with the $CaCO_3$ channel gates of MSN to release the encapsulated DOX inside the mesoporous structure and produce CO_2 gas, causing water penetration into the PLLA fibers and accelerating the DOX release. B,C) Reproduced with permission.[247] Copyright 2015, Elsevier.

5.1.2. Extended Release

In extended release systems, the drug is released at a constant or variable slow rate over an extended time.[99,132] In this system, different phenomena such as diffusion,[33] decomplexation,[178] ion exchange,[177] dissolution, erosion, swelling, and degradation[245] can control the release rate.[246] In systems such as fibers loaded with encapsulated drugs[173] or hollow fibers,[92] the main mechanism of the release is based on the diffusion; therefore, the concentration gradient and diffusion coefficient govern the release rate. The release rate of inclusion complexes is controlled by k_c and k_d, the complexation and decomplexation constants, respectively,[214] and is usually depended on the interactiveness of drug as the guest molecule and host molecule.

In some cases, the release rate is regulated by the dissolution rate of the macromolecular structure in which the drug is loaded. Examples of such systems are fibers loaded with encapsulated drugs in which the matrix is soluble in the surrounding media. Some drugs can bind to ion-exchange materials as explained in Section 4.5. In ion-exchange textile systems, the eluting rate of the bioactive compounds attached to ion-exchange fibers is controlled by the ability of the textile surface to preferentially exchange counter-ions, the concentration of the surface ion-exchange groups, the ionic characteristics or the pH of the local medium, and the type of the ion-exchange material. In addition, erosion and degradation governed structures benefit from a biodegradable macromolecule that is gradually eroded or degraded and as a result, drugs are eluted.

The fiber erosion or degradation rate regulates the release rate of the drugs.[246] However, dissolution, ion-exchange, erosion, and degradation can be the mechanism behind triggered or delayed release too.[27,132] Volokhova et al. irradiated electron beam on paracetamol-loaded PCL electrospun meshes covered with pure PCL nanofibers. The combination of e-beam irradiation and the fibrous layer resulted in an extended release profile with no burst effect and enhanced drug release quantities over time since e-beam reduced the PCL molecular weight and the multilayers created diffusion barrier and declined swelling.[83]

5.1.3. Triggered or Delayed Release

A trigger/stimulus or time can determine the release of the drug in these systems. Therefore, the type of release can be immediate or extended based on the material and design. The release can be triggered by stimuli such as light, pH, temperature, ionic strength, sonification, erosion, degradation, and dissolution. Therefore, consecutive release profiles over a longer period can be achieved.[27,132] Zhao et al.[247] fabricated a smart and tumor pH-trigged PLLA electrospun fabric for inhibiting cancer relapse. Mesoporous silica nanoparticles (MSNs) were loaded to the fibrous structure to extend the anticancer drug doxorubicin (DOX) release, which was physically adsorbed onto MSNs. $CaCO_3$ inorganic caps were incorporated to temporarily block the pores of MSN loaded nanofibers until the pH change triggered the drug release. $CaCO_3$ caps were stable at physiological pH of 7.4; however, in an acidic media where protons were released from the tumor cells (pH < 6.8), $CaCO_3$ gates dissolved into biocompatible Ca^{2+} (cations) and released CO_2 gas. This phenomenon led to increased water penetration into the PLLA nanofibers and accelerated DOX release. This pH-dependent drug-loaded fibrous system can inhibit long-term exposure of drugs to healthy cells by preventing drug release at non-acidic conditions.

In this study, three main groups of PLLA fibers co-electrospun with DOX (Figure 6B-x,w,x'), MSN-DOX (Figure 6B-y,v,y'), and MSN-DOX-$CaCO_3$ (Figure 6B-z,u,z') were fabricated, and SEM, transmission electron microscopy (TEM), and energy-dispersive X-ray (EDX) were used to analyze the morphology of fibrous structures and the effect of drug loading on the fiber structure. Comparing the release profiles of DOX loaded fibers (Figure 6C-I) with the electrospun $CaCO_3$ caped fibers (Figure 6C-II) at various pHs demonstrated significant pH-dependent drug-eluting behavior. Moreover, sustained drug release over a period of 40 d from MSN-DOX-$CaCO_3$ fibers was observed only when the environment became acidic (Figure 6C-III). Finally, this example showed the importance of the triggered release in providing a sustained drug release while minimizing the damage to untargeted tissues.

5.2. Kinetics of Drug Release

The drug release kinetics from fiber-based structures is influenced by various mechanisms, vigorously relying on polymer–drug system properties and interactions, such as physicochemical characteristics of the drug, fiber spinning and loading methods, the solubility of the drug in the release medium, and the interactions between the loaded material and the target tissue.[4] Various mass transport mechanisms, including diffusion, swelling, dissolution, erosion, or a combination of them governs the drug extraction from a polymer matrix. Generally, hydrophilic drug release occurs through simple diffusion, whereas water-insoluble drugs release happens by swelling or erosion of the macromolecule matrix.[248] Mathematical models have been proposed to describe, quantify, and predict the kinetics of drug release. Therefore, fitting experimental data of drug release with various mathematical models is a key to understanding how the polymer–drug systems affect the transport mechanisms to tune therapeutic parameters, such as the drug dose, release rate, and the release time.

The drug dissolution rate in a medium can be explained by:

$$\frac{dC}{dt} = DAh\left(C_s - C_{(t)}\right) \quad (1)$$

As dC/dt is the dissolving rate, D the diffusion coefficient of the drug, h the width of diffusion path, A the surface area of the subjected polymer to medium, C_s the saturated amount of dissolvable drug, and $C(t)$ the drug concentration in the release medium at time t.

The drug release profile can be obtained by plotting the drug release fraction versus time:

$$Q_{(t)} = \frac{M_t}{M_{tot}} \quad (2)$$

$Q_{(t)}$ is the cumulative fraction, M_t is the amount of drug at time t, and M_{tot} is the total amount of loaded drug.

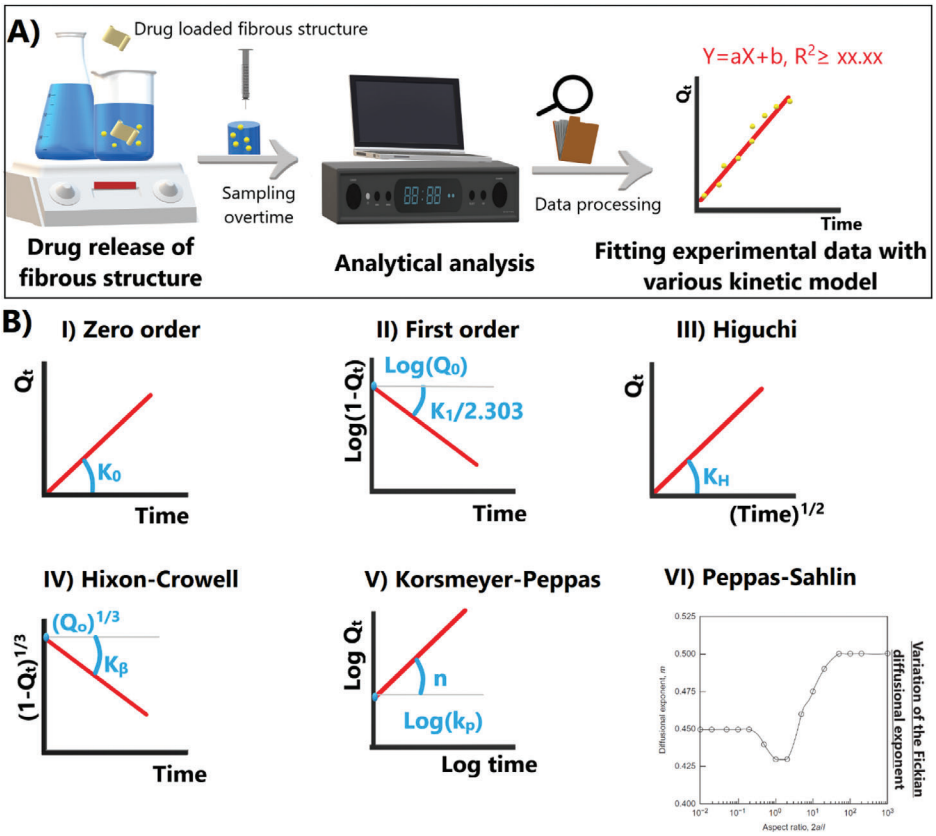

Figure 7. Representation of the release kinetics models. A) Evaluation process of experimental drug release data with empirical models. B) linearized plots of most common release model drugs, I) Zero-order model, II) First-order model, III) Higuchi simplified model, IV) Hixon-Crowell model, V) Korsmeyer-Peppas (power-law model), and VI) Peppas-Sahlin, variation of the Fickian diffusional exponent, m, with the aspect ratio, $2a/l$, where $2a$ is the diameter (width) and l is the thickness (height) of the matrix. Reproduced with permission.[42] Copyright 2015, Elsevier.

The release profiles of each polymer–drug system can be assessed and explained by a mathematical model. The statistical coefficients, namely the higher coefficient of determination (R^2) and the lower AIC (Akaike Information Criterion), are used to check the accuracy of the model to justify the experimental data. Therefore, the mechanisms with the highest potential to control the drug release can be recognized from the best fit model (**Figure 7**A). Several common mathematical models applicable for macromolecule systems, zero-order, first-order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, and Peppas-Sahlin, are reviewed in the following sections with an emphasis on drug-eluting fibers.

5.2.1. Zero-Order Model

Zero-order kinetics is an "ideal" linear drug release profile. The eluting rate is independent of the drug concentration in the system and remains constant over time.[249,250] This model can be explained by:

$$Q_{(t)} = k_0 t_n \tag{3}$$

where $Q_{(t)}$ is the cumulative fraction of the drug released at the time t, k_0 is the constant rate or apparent dissolution rate, and n is geometrically dependent, 1.0 for a thin film, 0.89 for a cylinder, and 0.85 for a sphere. In some studies, the researchers have considered electrospun meshes as thin films, while for single microfibers, the cylinder geometry seems to be more accurate.

A graphical representation of the model is shown in Figure 7B-I. Zero-order release typically happens in transdermal or osmotic systems and for prolonged-release from a system that does not break down when loaded with a very low soluble drug. Ahadi and co-workers[251] fabricated electrospun vancomycin hydrochloride (vanco HCL) loaded PLLA fibers. The electrospun fibers were added to a silk fibroin/oxidized pectin hydrogel as a secondary structure where drug-loaded hydrogel/fiber complexes were fabricated. During the first day (24 h), the release amount of vanco HCl from drug-loaded hydrogel was 35.97% while from hydrogel/fiber composite was 13.83%. The drug release mechanism in such a gel-fiber system can be complicated and affected by parameters such as polymer degradation, hydrogel swelling, and hydrophobicity or hydrophilicity of the fibers. In order to evaluate the kinetics model, maximum linearity was considered to check the accuracy of the model. The drug-loaded hydrogel/fiber proved to have zero-order release with $K_0 = 3.307$ and $R^2 = 0.98$.

5.2.2. First-Order Model

First-order release kinetics is corresponding to the amount of the loaded drug in the matrix. This model results in constant

release overtime, and the rate is only dependent on the initial drug concentration.[252] The cumulative released fraction can be described by:

$$Q_{(t)} = 1 - \exp\left(-k_1 t\right) \tag{4}$$

or

$$\log\left(1 - Q_{(t)}\right) = k_1 \cdot \frac{t}{2.303}$$

where (1 - $Q_{(t)}$) indicates the residual fraction of drug at the time t in the system, and k_1 is the first-order constant (Figure 7B-II).

The first-order kinetics is favorable for the sustained release of the drug delivery systems. For example, it can be observed in systems consisted of water-soluble drugs loaded in a porous matrix, where the release rate is only controlled by diffusion or dissolution.

Painuly et al.[172] studied a drug delivery system based on gelatin nanofibers for two contraceptive drugs comprising levonorgestrel (LNG) and ethinylestradiol (EE). In the case of individual loading of the drugs, it was observed that the release of EE was altered by the initial content of the loaded drug, whereas no significant difference was seen for the LNG with a sustained release of 30–35 µg day^{-1}. This could be attributed to the hydrophobic nature of LNG as no significant difference in morphology of the loaded fibers with increasing the LNG dosage was observed. On the other hand, fibers loaded with both LNG and EE showed a minor burst release on the first day, followed by a sustained release of both drugs up to 7 d.

In addition, LNG release was ≈4–5 fold increased in dual drug-loaded samples compared to single LNG loaded fibers due to the combination of drugs. In vitro LNG release kinetics could be fitted by zero-order and first-order model with $R^2 \geq 0.99$ for both models. EE/gelatin nanofibers were described convincingly by zero- and first-order models with R^2 in the range of 0.93–0.97. In the case of dual drug loading, the release of LNG and EE was described by zero-order and first-order model for LNG ($R^2 \geq 0.99$), whereas Higuchi and Korsmeyer-Peppas model, explained in the following section, could better describe the EE release ($n = 0.49$, $R^2 \geq 0.97$).

5.2.3. Higuchi Model

There was no mathematical model to explain the drug dissolution from matrix systems until the 1960s. One of the earliest models has been described by Higuchi[253] which was initially effective only for a planar matrix but later was adjusted to be applied to different geometries and matrices.[254] Higuchi model is based on Fick law and describes the release kinetics of a hydrosoluble drug dispersed in a homogeneous solid matrix. Drug release happens by Fickian diffusion of the release medium and the drug within the pores macromolecule structure. The model is justifiable if the diffusion coefficient or matrix geometrical dimensions of the matrix are persistent over time,[253] meaning that it does not apply to cases such as swellable or soluble delivery systems.

The cumulative released fraction in this model is:

$$Q_{(t)} = \frac{\sqrt{D\epsilon}}{\tau} \times \left(2m_{\mathrm{d}} - \epsilon S_{\mathrm{d}}\right) t \tag{5}$$

where ϵ is the polymer porosity, τ is the capillary tortuosity factor, m_{d} is the initial amount of the drug, and S_{d} is the solubility of the drug. Tortuosity is used to describe diffusion and fluid flow in porous media and it is the proportion of radius and branching of the pores and canals in the matrix.

This model is simplified as:

$$Q_{(t)} = k_{\mathrm{H}} \sqrt{t} \tag{6}$$

where K_{H} is the release constant of the Higuchi model. As expected from Fick's law, the amount of released drug is proportional to the square root of time. A graphical representation of the model is shown in Figure 7B-III.

In a study by Pisani et al.,[255] gentamicin sulfate (GS) was encapsulated into polylactide-co-polycaprolactone (PLA-PCL) electrospun nanofibers. Due to the antibacterial activity of the GS-loaded fibrous meshes, they were used for the topical controlled drug delivery for treating infected skin and gum or for preventing infection in bone surgery. The kinetic release of the drug-loaded fibers could be predicted and explained by the Higuchi kinetic model, both in dynamic and static conditions ($R^2 \geq 0.9$).

5.2.4. Hixson-Crowell Model

The Hixson-Crowell model is based on two assumptions; drug release is limited only by drug dissolution rate, and the matrix erosion happens by decreasing the dimension of the matrix while keeping the initial shape constant.[256]

$$\sqrt[3]{M_0} - \sqrt[3]{M_t} = k_{\mathrm{HC}} t \tag{7}$$

where M_0 is the initial amount of the drug in the system. The remaining drug in the system at time t is M_t, and k_{HC} is the constant of incorporation, which connects the surface and the volume of the drug.

The Equation (7) could be simplified by dividing it by $\sqrt[3]{M_0}$:

$$\left(\sqrt[3]{1 - Q_{(t)}}\right) = 1 - k_\beta t \tag{8}$$

where (1-$Q_{(t)}$) is the remaining fraction of drug within the polymer matrix, and k_β is a release constant (Figure 7B-IV).

Hixson-Crowell model could satisfactorily represent the release kinetics of curcumin (CUR) loaded in zein (zein-CUR) electrospun fibers, where the morphology and the size of fibers were strongly dependent on CUR loading dosage. This was mainly due to the hydrogen bonding between CUR and the fibers and a slight increase in the T_{g} of the zein matrix. In the case of 20% w/w CUR loading, around 70% of the drug was released in 180 min. Furthermore, a higher dosage loading caused a faster release rate due to the diffusion-controlled release behavior of the system which was derived from CUR dosage change.

By investigating several models for three different CUR loading dosages, the first-order model exhibited the highest value of R^2 (0.9940–0.9969), indicating that the CUR diffusion in fibers might be a rate-limiting step. Furthermore, the release profile was explained by Hixson–Crowell model with a relatively high R^2 (0.9638–0.9896), which additionally clarified that the CUR release from the fibers was mainly based on the diffusion rather

than the matrix erosion mechanism. Finally, the system was evaluated for antibacterial activities using *Escherichia coli* and *Staphylococcus aureus* bacteria. The outcomes showed good antibacterial activity toward the targeted bacteria where the bacterial inhibition capability improved with the increased CUR contents.[257]

5.2.5. Korsmeyer–Peppas Model

The Korsenmeyer-Peppas, as a semiempirical model, explains the exponential relationship between the release and the time. It is mainly used to inspect the release of the drug from a hydrophilic polymer-based system.[258,259] The model is expressed by:

$$Q_{(t)} = \frac{M_t}{M_\infty} = K_{KP} t^n \quad (9)$$

where K_{kp} is the constant accounting for the dimensional properties of the system, also assessed as the release rate constant, and n is the exponent of release related to the drug release mechanism as shown in Figure 7B-V. This model can be used when the release mechanism is unknown or when more than a known mechanism is involved. The dominant physical mechanism of drug release is recognized by obtaining the value of the exponent n based on the optimal fit with experimental data (for $(t) < 60\%$) and the system dimension.

Fickian diffusion or non-Fickian mechanisms alter with the rate of solvent diffusion. In the case of $n = 0.45$ or Fickian diffusion, the typical molecular diffusion of the drug occurs due to a chemical potential gradient. In other words, the rate of solvent diffusion is much slower than polymer relaxation (swelling or/and erosion of matrix) time. This case is similar to the model described by Higuchi for Fickian diffusion. However, in non-Fickian mechanisms, when $0.45 < n < 0.89$, the release is controlled by both diffusion and macromolecule relaxation (swelling or erosion) since solvent diffusion and polymer relaxation occur at comparable time rates. When $n = 0.89$, the mechanism is governed by polymer relaxation, which is similar to zero-order kinetics. Finally, in the case of $n > 0.89$, an extreme form of transport, called non-Fickian diffusion, driven by the acceleration of solvent penetration occurs.

Generally, these models have been used to study drug delivery from sources such as tablets, hydrogels, membranes, and fibers. The water molecules in majority of the studied systems are the initiators of the drug release process through swelling of the loaded polymer matrix.[260,261] Furthermore, the rate-restricting phenomena for a hydrophilic drug loaded in water-insoluble and non-erodible fibrous structure, such as CA nanofibers, is diffusion through typically a hydrophobic hindrance.[262]

For instance, gallic acid (GA) was microencapsulated in PCL by the solvent vaporization, and the homogenous PCL–microspheres were applied onto textile substrates of cotton and polyamide. GA has shown biological activities, including antioxidant, antityrosinase, antimicrobial, anti-inflammatory, and anticancer properties.[261] The apparent diffusivity, D, was obtained using the Fick's second law, Higuchi model (Equation 6). The kinetic studies done using Korsenmeyer-Peppas equation proved that the hydrophobicity and affinity of the textiles and GA affected the eluting mechanism. The apparent diffusion coefficients were predicated for plane surfaces. For cotton, an explicit Fickian diffusion was obtained ($n \approx 046$, $n \leq 0.5$); however, for polyamide, the diffusion was anomalous ($n \approx 0.63$, $0.5 < n < 1$). Moreover, no differences were found in the K_{kp} (Equation 12), which is the constant comprising the dimensional properties of the system.

5.2.6. Peppas-Sahlin

Peppas-Sahlin is a power-law model originated from Korsenmeyer-Peppas (Equation 12) which take into account the role of two physical mechanisms: diffusion and macromolecule relaxation.[263] This model is expressed by:

$$Q_{(t)} = \frac{M_t}{M_\infty} = K_F t^m + K_R t^{2m} = F + R \quad (10)$$

where K_F is the diffusion constant, K_R the relaxation constant, and m is the Fickian diffusion exponent of a matrix of any dimensional shape (cylinders, tablets, and films).

The model assumes that drug is eluted from any matrix, disregarding of its dimensional structure shape, consists of a Fickian and a relaxation term. If the Fickian character can be stated as a function of t^m, the polymer relaxation role can be indicated as a function of t^{2m}. The Fickian diffusional exponent, m, differs with the ratio between the width and height of the matrix in which Peppas and Sahlin defined it as $2a/l$, where $2a$ is the width (diameter) and l is the height (thickness) (Figure 7B-VI). The drug release by the Fickian mechanism, F, is obtained by:

$$F = \frac{1}{1 + \frac{K_R}{K_F} t^m} \quad (11)$$

And the ratio of relaxation over Fickian is:

$$\frac{R}{F} = \frac{K_R}{K_F} t^m \quad (12)$$

PLA/ polyvinyl alcohol (PVA) core–shell nanofiber scaffolds loaded with BMP-2 proteins to enhance the recovery of alveolar bone tissue were used in a study. Albumin was utilized as a model drug to optimize the fiber production and loading parameters. Fabricated core–shell nanofibers released 30% of the loaded albumin while PVA monolithic fibers released 92% of the encapsulated albumin in 1 h. Peppas-Sahlin could sufficiently explain the release of albumin ($R^2 > 0.98$, $m = 0.45$), suggesting that the albumin release occurred through the Fickian diffusion process. Based on the in vitro results, cell viability, adhesion, and proliferation were observed.[264]

Other models such as Hopfenberg,[265] Gallagher–Corrigan,[266] Weibull,[267] have been also utilized in different research studies to predict the drug release from various drug-loaded materials. In summary, these models are valuable tools to discover the exact mass transport and quantitative estimation of drug release. Using these models, scientists are able to design a controlled and tunable release from drug-eluting systems in various applications. Examples of the applications that have used the drug-eluting systems are reviewed in the next section.

6. Applications

A wide spectrum of drug-loaded textiles has been designed to deliver various bioactive agents in various manners. Numerous manufacturing processes alongside the loading methods of various pharmaceutical agents have made the drug-eluting fibrous system an interesting candidate for three main application areas of wound care, tissue engineering, and transdermal drug delivery system (**Figure 8**A).

6.1. Wound Care

An ideal wound dressing has characteristics such as oxygen and water vapor permeability, resistance to the penetration of microorganisms, and antimicrobial activity to prevent infection. Furthermore, it should be easy and comfortable to apply to the wound, minimize the pain, and inhibit bleeding.[132,268] The delivery of bioactive agents has a significant role in the wound-healing process. This includes a wide range of compounds and measures including antimicrobials to avoid or heal infection, growth factors to help cellular proliferation, cleansing or debriding agents for eliminating necrotic tissue.[4] The biomaterials used for wound dressing should also be biocompatible and assist the growth of skin cells. Woven and nonwoven textiles that have small pore sizes to permit controlled fluid transport and resist the infiltration of infectious microorganisms can be sued for this application. Moreover, both degradable and nondegradable materials have been used for the production of wound dressings.[4,132]

Degradable polymers are suitable candidates to be used as skin scaffolds, whereas nondegradable polymers can be employed as temporary wound dressings.[269] As an example, polyurethane (PU), as a nondegradable polymer, has been used for wound dressing application due to its elastic properties.[270] However, it is also possible to synthesis PU in a degradable form, such as poly(ester-urethane) urea (PEUU), which could be used as a scaffold for skin tissue engineering.[271] If an individual material cannot satisfy the requirements of the application, a combination of various materials, such as degradable and nondegradable, can enhance the firmness, spinnability, strength, wettability, and bioactivity of the fibrous system.

Medical device-related infections and antibiotic-resistant issues require anti-infective materials to preserve wounds and medical devices.[272] In this direction, utilization of chitosan as a base material for antimicrobial wound dressings was explored. A tricomponent antimicrobial nanofiber composite from chitosan/polyvinyl alcohol/silver nanoparticles was developed via electrospinning,[273] where green chemistry principles were applied. Chitosan was employed as a capping agent and glucose as a reducing agent for silver nanoparticles (25 nm diameter). Nanofibers with 150 nm average diameter of regular cylindrical shape morphology were obtained upon blending chitosan/ silver nanoparticles with PVA and cross-linking with glutaraldehyde. The release profile of silver ions from nanofiber mats was assessed by atomic absorption. The nanofiber mats attained sustainable release behavior over 7 d and exhibited high antibacterial activity against *E. coli* at low silver nanoparticle loads. In another study, the chemical modification of chitosan using iodoacetic acid was evaluated, where 1-ethyl-3(3-dimethylamminopropyl) carbondiimide hydrochloride with hydrochloric acid (EDAC·HCl) and *N*-hydroxysuccinimide (NHS) coupling was employed.[274] The chitosan iodoacetamide derivative exhibited bactericidal properties when tested against *E. coli*. It is thought that the incorporation of iodine active terminal into a chitosan backbone resulted in an increase in the antibacterial effectiveness by disulfide bond development with the proteins of the bacterial outer membrane.

Electrospun mats were made out of gelatin and incorporated with polyhydroxy antibiotics. These antibacterial drugs have a various number of hydroxyl groups in order to make strong interfacial bonds to gelatin by the aid of in situ crosslinking with polydopamine (pDA). Vancomycin (Van) loaded fibers showed to have high mechanical properties and to modulate cytokine production essential in stopping sepsis after burn injury.[275] The direct electrospinning of Van-loaded gelatin on cotton gauze bandages eliminated structural irregularity and provided an easy to wrap wound dressing. The mesh was crosslinked, and its efficacy was investigated in white pig models with similar pathophysiology of burn wounds to humans. The result was compared to untreated wound, nonloaded mats of Gel_pDA, and silver-based wound dressings called Aquacel Ag. It was observed that encapsulation of Van enhanced the wound closure and led to faster re-epithelialization, decreased inflammation, and higher keratinization (Figure 8B-I–III). Moreover, pDA crosslinking did not influence the wound healing process. Van_Gel_pDA (Figure 8B-IV-z) showed less number of inflammatory cells compared to the untreated (Figure 8B-IV-x) and non-loaded mat (Figure 8B-IV-y), and exhibited signs of connective tissue remodeling. However, silver loaded dressing proved to have fewer inflammatory cells and a confluent epithelial layer compared to untreated, non-loaded and loaded wound dressings (Figure 8B-IV-w).[276]

Microfibers have also been utilized to fabricate wound care products. Melt spun fibers from acrylonitrile-co-1-vinylimidazole (AN/VIM) copolymer to release nitric oxide (NO) were fabricated to enhance the wound healing process. NO plays an important role in stimulation of collagen deposition and angiogenesis during the wound healing process. A 12–24 h delay in the NO release showed to be ideal in the wound healing process as this factor could accelerate the transition of the inflammatory to the proliferative phase. To produce the NO donating group, the diazeniumdiolate (NONOate), melt-spun AN/VIM fibers were reacted with NO at a constant pressure of 4 atm for 1 h. As a result, the NONOate formed on acrylonitrile segments of fibers, where each NONOate released two molar equivalents of NO upon reaction with a proton source. In addition, to extend the release time of NO-loaded AN/VIM fibers, they were dip-coated in a solution of PCL and chloroform (2 w w^{-1}%). The coating created an evenly distributed porous layer along the entire surface of the fibers. After 3 days, the PCL coated melt-spun AN/VIM copolymer fibers released a total of 84 μmol NO g^{-1}, while uncoated fibers released 91 μmol NO g^{-1} in 3 h.[277]

Eventually, modification of the experimental set-up in terms of the fiber production methods, the type materials and drugs, and the employed release mechanisms leads to well-structured nano- or microfibrous textiles with a high surface-to-volume ratio and interconnected pore structures to support tissue regeneration and remodeling, and to assist gas exchange and bioactive agents supply. A review of studies in which drug-eluting constructs are used for wound care application is summarized in **Table 2**.

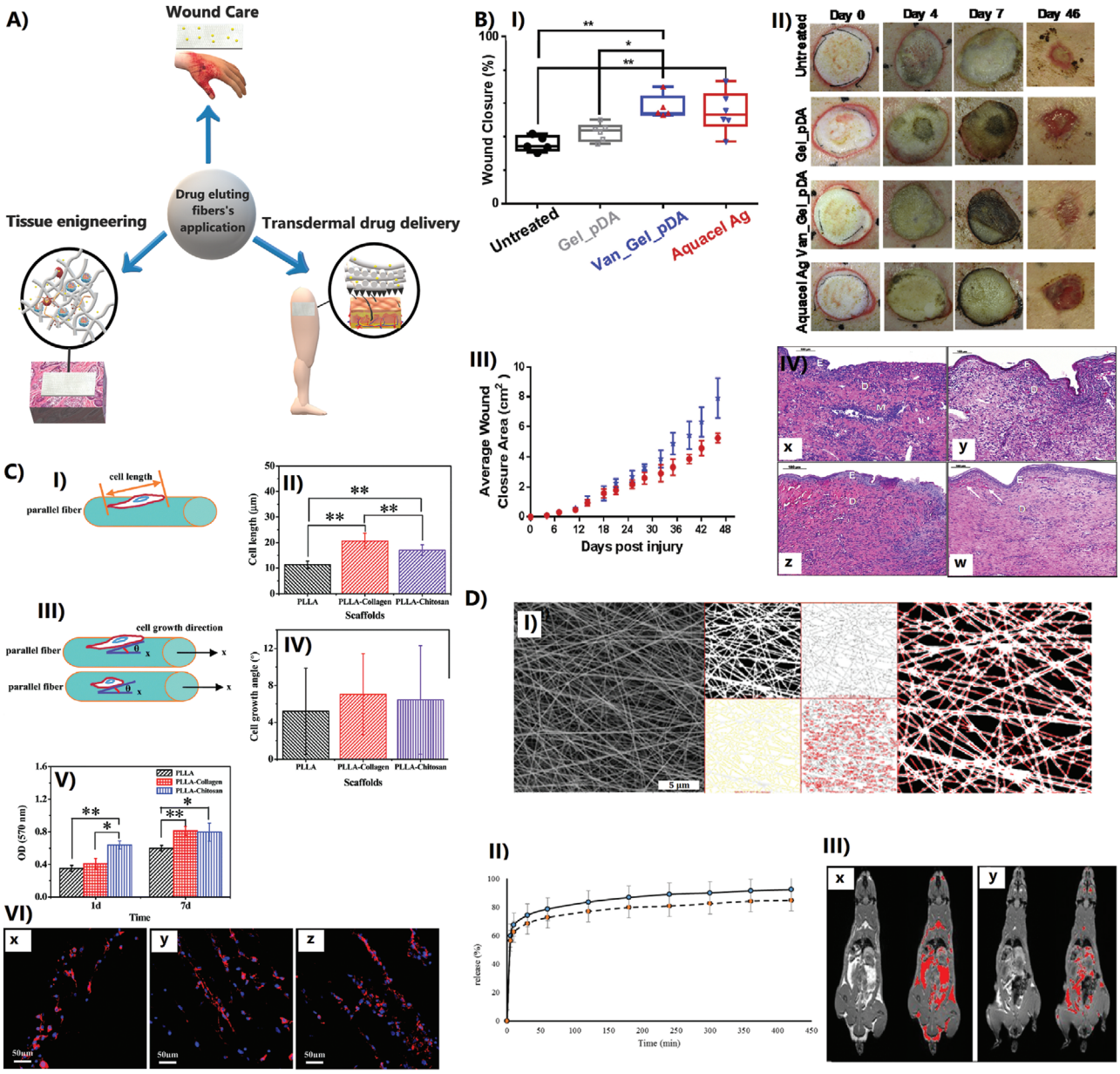

Figure 8. Applications of drug-loaded fibrous structures. A) Wound care, tissue engineering, and transdermal drug delivery applications using drug-loaded fibers. B) In vivo wound healing efficacy of antibacterial wound dressing made of Van_Gel_pDA in a pig model, (I) Relative wound closure of different groups at 46 d post-injury. Obvious impact of Vanco_Gel_pDA on wound closure rate in comparison with non-loaded nanofibers of Gel_pDA and untreated wounds. (II) Images indicating the condition of the wounds before the debridement at different days (0, 4, 7, 46). The wound surface showed moderately dry and decreased pus creation in Van_Gel_pDA mats and Aquacel Ag cured wounds, (III) Average wound closing (cm^2) for Gel_pDA (red bars) and Van_Gel_pDA (blue bars) medicated wounds proved that loading the antibiotics enhanced the wound healing and re-epithelialization, (IV) Histological changes during wound healing after burn injury, (x) Untreated control; Injuries treated with (y) Gel_pDA, (z) Van_Gel_pDA, and (w) Aquacel Ag. Epidermis (E), dermis (D), inflammatory cells (M), and the blood vessels (arrows) are indicated in the figure. Scale bar = 100 μm. Reproduced with permission.[276] Copyright 2017, Elsevier. C) (I) Schematic representation of the cell size, (II) cell size on various categories of scaffolds ($N = 10$), (III) schematic illustration of the cell promotion angle between the cell growth direction and the fiber parallel direction (x axis), (IV) cell proliferation angle on various scaffolds ($N = 10$), and V) Cell viability ($N = 3$). * and ** exhibited remarkable difference at $p < 0.05$ and $p < 0.01$, respectively, (VI) CLSM images of osteoblasts on a) PLLA, b) PLLA–collagen, and c) PLLA–chitosan aligned scaffolds, respectively. Cell nuclei are shown in blue and actin fibers in red. Reproduced with permission.[297] Copyright 2013, the royal society of chemistry. D) (I) PVA nanofibers fabricated utilizing optimum point parameters and processed SEM in similar conditions, (II) Curcumin loaded release into PBS buffer (dashed curve) and NaCl solution (solid curve), (III) Adipose tissue imaging using MRI in (x) untreated rats versus (y) treated rats by the transdermal patch. Reproduced with permission.[318] Copyright 2018, Elsevier.

Table 2. Drug eluting fibrous systems used in wound care applications, tissue engineering, and transdermal drug delivery.

Application	Material	Drug	Spinning method	Loading method	Type of release	Transport mechanism	Release kinetics	Remarks and outcome
Wound care	Polylactide-co-polycaprolactone	Gentamicin sulfate	Electrospinning	Encapsulation	Extended	Fickian diffusion and polymer swelling	Higuchi ($R^2 = 0.97$)	Effective against *S. aureus* and *E. coli* bacteria.[255]
	Polyvinyl alcohol/chitosan	Antibacterial peptide OH-CATH30	Electrospinning	Encapsulation of carboxymethyl chitosan nanoparticles loaded with antibacterial peptide OH-CATH30	Extended	–	–	Dual antibacterial activity due to the presence of chitosan and peptide OH-CATH30 against *E. coli* and *S. aureus*, with promoted wound healing functionality.[85]
	Nylon 6.6 DuPont type 200 woven fabric (PA)	Gallic acid microencapsulated in poly-ε-caprolactone	–	Coating (pad-drying process)	Extended	Fickian diffusion and retention of the microspheres on the surface	Korsenmeyer–Peppas ($n = 0.46$, $R^2 = 0.88$)	Drug-delivery (GA-PCL) system for medical and cosmetic textiles.[261]
	Zein	Curcumin	Electrospinning	Encapsulation	Extended	Diffusion (concentration depended)	First-order R^2 (0.9940–0.9969) Hixson–Crowell R^2 (0.9638–0.9896)	The antimicrobial applications of zein-CUR nanofibers showed to prevent bacterial growth.[257]
	Chitin	–	Wet spinning	–	–	–	–	Nonwoven chitin fabrics maintained the intrinsic structure of α-chitin and enhanced wound closure rate.[319]
	Acrylonitrile-co-1-vinylimidazole (copolymer)	Nitric oxide	Melt spinning	Release of NO was controlled with PCL coating	Triggered	–	–	By PCL coating, the release of nitric oxide was extended.[277]
Tissue engineering	Poly (L-lactide) fiber and silk fibroin/oxidized pectin hydrogel	Vancomycin hydrochloride	Electrospinning	Encapsulation	Extended (sustained)	Degradation, swelling, and diffusion	Zero order ($R^2 = 0.98$)	Loading of aminolyzed PLLA–drug fibers in hydrogel reduced the swelling ratio, enhanced the mechanical properties, and led to a more sustainable release of vanco HCl.[251]
	Polylactide/ polyvinyl alcohol	Albumin BMP-2	Coaxial electro-spinning	Encapsulation	Extended	Diffusion and polymer chain relaxation	Peppas-Sahlin ($R^2 > 0.98$, m = 0,45)	BMP-2 loaded coaxial electrospun PLA/PVA scaffolds guided regeneration of bone.[264]
	Three-arm branched-star PCL	Hydroxyapatite nanoparticles (HNPs) and clodronate (CD)	Wet spinning and electro-spinning	Encapsulation	–	–	–	Formation of defects induced by loading were minimized by optimizing the spinning conditions.[296]
	Poly-L-lactide	Collagen, chitosan	Melt-spinning	Coating	–	–	-	Collagen coated melt-spun fibers enhanced the viability, adhesion, alignment, and migration of osteoblasts in vitro.[297]

(*Continued*)

Table 2. (Continued).

Application	Material	Drug	Spinning method	Loading method	Type of release	Transport mechanism	Release kinetics	Remarks and outcome
	Polyacrylonitrile	Acyclovir	Electrospinning	Bioconjugation	Extended	Fickian diffusion	Korsmeyer-Peppas ($n = 0.26$, $R^2 = 0.96$)	Oxidized chitosan modified polyacrylonitrile loaded with acyclovir showed controllable sustained-release profile of acyclovir with improved cell adhesion and proliferation of adipose-derived stem cells.[320]
	Poly-L-lactide	DNA plasmid	Electrospinning	Encapsulation	Extended	–	-	PLA electrospun meshes impregnated with DNA plasmid and pBMP-2 genes and incorporated into gelatin methacryloyl and thiolated chitosan hydrogel system promoted bone repair and regeneration.[321]
Transdermal drug delivery	Gelatin	Levonorgestrel (LNG), ethinylestradiol (EE)	Electrospinning	Encapsulation	Extended (with first day burst effect)	Fickian diffusion	Both individual and dual loading of LNG zero-order and first-order model ($R^2 = 0.99$), individual loading of EE first-order model ($R^2 = 0.93$–0.97), dual loading of EE Higuchi model ($R^2 \geq 0.97$)	A high encapsulation efficiency (≈90–100%) and drug loading (>90%) were obtained. The fibrous construct showed to be biocompatible and both drugs were permeable through the filter membrane.[172]
	Cellulose	Ibuprofen	Electrospinning	Coating (immersing)	Immediate	Fickian diffusion	Korse meyer-Peppas (2% w/v, $n = 0.42$ and $R^2 = 0.93$; 3% w/v, $n = 0.26$ and $R^2 = 0.99$)	A micro-/nanofibrous nonwoven made out nonderivative cellulose showed the potential to be used for transdermal applications as a biocompatible construct.[317]
	Polycaprolactone	Vitamin B12	Electrospinning	Encapsulation and plasma treatment	Extended	Polymer swelling	Higuchi	The drug release rate of hydrophobic nanofiber impregnated with the hydrophilic drug was controllable by plasma treatment time which increased the hydrophilicity of the surface.[322]
	Poly(lactic-co-glycolic acid)	Daidzein	Electrospinning	Encapsulation	Extended	Non-Fickian diffusion	Kormeyer-Peppas ($n = 0.52$, $R^2 = 0.99$)	Core–shell nanofibers of poly(lactic-co-glycolic acid) were loaded with daidzein nanostructured lipid carriers azone proved to have a sustained drug delivery. In vivo tests showed an increase in skin permeation of daidzein efficiently without skin irritation.[323]
	Psyllium husk mucilage	Paclitaxel	Electrospinning	Encapsulation	Extended	–	–	Paclitaxel loaded poly (bis (carboxyphenoxy) phosphazene)-cholic acid micelles were loaded in the psyllium husk mucilage to form the novel stimuli-responsive core–shell nanofibers. The meshes can actively inhibits the growth of MCF-7 cancer cells and provide a safe cancer therapy.[324]

6.2. Tissue Engineering

Tissue engineering requires the generation of biological alternatives to restore and regenerate damaged tissues.[278,279] Tissue engineering involves utilization of a biodegradable matrix, so-called scaffold, sometimes loaded with pharmaceutical agents and/or cells in order to assist the three-dimensional tissue development.[280–283] Drug-eluting scaffolds have been fabricated based on nonwoven and woven structures. Electrospun nonwovens have been well studied for regenerative medicine and tissue engineering applications since an ultrafine fibrous network with high surface-to-volume ratio resembles the natural extracellular matrix.[132,284–286] Nonwoven fabrics with the capability to deliver bioactive components, such as antibiotics, growth factors, and chemotherapeutic agents, have proven to accelerate or inhibit certain activities during tissue regeneration and remodeling.[4]

Release of encapsulated bone morphogenetic proteins growth factor from electrospun composite scaffolds made of silk fibroin/PEO or poly(D,L-lactide-co-glycolide)/hydroxylapatite (PLGA/HAp) accelerated osteogenesis and nerve regeneration processes.[287,288] In another study conducted by Bide and coworkers, endothelialization was promoted to reduce thrombus formation by immobilizing vascular endothelial growth factor and an anticoagulant agent on the surface of the knitted polyester grafts.[289] Although electrospun constructs have been vastly used for tissue engineering applications, cell infiltration through the nanofiber is still the major limitation of this method due to their small pore sizes. Particle leaching and sacrificial nanofibers are the two proposed solutions to overcome this issue.[290] Removing long molecular polymer chains of sacrificial fibers might be more difficult compared to the leaching particles but leads to better interconnected pores between the fibers.[291]

Nonwoven wet-spun fibers from natural-based polymers, such as chitosan,[292,293] starch-based,[294] and PLLA,[295] have also been used for the fabrication of scaffolds. In a study, wet-spinning and electrospinning were used for preparing fibrous bioactive scaffolds to stimulate bone regeneration. The fibrous scaffold was made of a solution of biodegradable three-arm branched-star PCL, hydroxyapatite nanoparticles (HNPs), and clodronate (CDE), a bisphosphonate anti-inflammatory drug that has revealed effectiveness in the healing of different bone diseases, including osteoporosis and hyperparathyrosis. To introduce physical binding between CDE and HNP, Cde–HNP complex particles were developed to obtain a better control over drug release and enhance osteoconductivity due to the presence of the inorganic phase.

In both wetspun and electrospun nonwoven structures, addition of HNPs, CDE, or CDE-HNPs changed the morphology and caused aggregation of the particles that were not loaded into the fibers. In addition, in contrast to the unloaded fibers, the surface porosity of wet spun CDE–HNP loaded fibers were decreased, and the fibers did not exhibit binding at the bonding points. Formation of the defects induced by loading was minimized by optimizing the spinning conditions, mainly increasing the solution feed rate. Finally, it was suggested to study a system composed of a combination of the electrospun and wet-spun fibers in a modulated ratio into a multiscale fibrous structure to keep a balance between the material binding sites to the cell membrane receptors and the release kinetics.[296]

Melt spinning can be a helpful method to produce scaffolds in a scalable, rapid, and solvent-free process. For instance, melt-spun aligned PLLA fibers glued by 5% PLLA tetrahydrofuran solution were fabricated to obtain fiber-aligned scaffolds to imitate the morphology of collagen fibrils. The fibers were coated with collagen and chitosan to achieve the biochemical and surface-aligned topography cues. In the case of coated fibers, viability, adherence, length, and migration functioning of osteoblasts were enhanced in vitro. The aligned fibrous scaffold coated with collagen had the most significant cell length and migration rate, and the osteoblasts favorably relocated and adhered across the parallel fiber direction (Figure 8C-II).

However, the cell directional growth angles on the PLLA and coated fibrous scaffolds showed no significant difference (Figure 8C-IV). The cell viability on the coated fibers was higher than pure PLLA fibers after the first and seven days of measurement (Figure 8C-V). Confocal laser scanning microscopy proved that osteoblasts cells were adhered and grew on the fibers, while the untreated fibers had weaker interaction with the cells due to the presence of a random and irregular distribution of actin fibers. Coated fibers displayed more robust cell-substrate interaction, and stressed actin fibers were established in the cells, specifically in the fibers coated with collagen (Figure 8C-VI). This indicates the potential of the coated fibrous constructs as a suitable biomimetic microenvironment for osteoblast growth and bone regeneration.[297]

As a result, surface topography and morphology of the fiber scaffolds, such as diameter, pattern, and pore size, have an essential role in regulating cell behaviors.[281,298,299] In general, the larger specific surface area of the fibers will make a higher ratio of the functional groups of the polymer chains exposed to the tissue. Consequently, more accessible binding sites to cell membrane receptors are present to enhance cell adhesion and growth.[300] The aforementioned features also influence the solute transport mechanism, which will facilitate the drug release and the rate of material degradation.[301]

Although the electrospun meshes mimic the ECM structure and stimulate the tissue growth and remodeling, the pore sizes are usually in the nanometer scale and can hinder cell infiltration through the fibrous system, which leads to an undesired tissue growth besides the burst effect of the drugs due to the high surface-to-volume ratio.[80] This emphasizes the necessity of microfabrication processes, including wet- or melt-spinning. Ultimately, combining the advantages of micro and nanofiber production helps to obtain a fibrous construct with better properties required for tissue engineering applications. Table 2 provides examples of drug-loaded fibrous systems for tissue engineering application.

6.3. Transdermal Drug Delivery

Transdermal fibrous systems can deliver bioactive materials across the skin in a sustained manner.[302] However, not many commercial transdermal drug-eluting systems have been introduced. The reason is mainly due to the impermeability of the stratum corneum, the external layer of skin. Therefore, drug molecule size cannot exceed more than 400–500 Da, and should have a balance of lipophilicity, log octanol–water partition

coefficient around 2 to 3 ideally, to be incorporated into the bloodstream.[302,303] In the case of larger molecules, microneedles are mounted into transdermal systems so that the drugs can bypass the skin layers mechanically.[304,305]

To treat various diseases, including superficial nociceptive pains, such as myalgia and muscular pain, transdermal drug delivery methods have been developed based on fibrous structures. These fibrous drug delivery systems take advantage of the minimum required drug dosage and avoid nonspecific site toxicity. A wide range of release profiles for this application can be governed by varying different parameters such as bioactive agent/polymer ratio, fiber shape, diameter, morphology, and combination of micro and nanofibers.[4,306]

Nonwoven electrospun fibers have been loaded with bioactive agents using various loading procedures, such as encapsulation,[307,308] coaxial electrospinning,[309] and chemical or physical surface modifications.[310] Transdermal electrospun mats have been fabricated from natural-based polymers, such as CA, PLA, and PCL. The fibrous constructs for treatment of local muscular pain and inflammation were loaded with various bioactive agents including nonsteroidal anti-inflammatory drugs (NSAID), such as naproxen, indomethacin, ibuprofen, and sulindac,[311] vitamins, such as vitamin A and E,[310] topical disinfectants, such as chlorhexidine,[312] and antibiotics and antimicrobial agents, such as amoxicillin,[313] tetracycline hydrochloride,[314] ornidazole,[168,315] and N-halamin.[316]

Cellulose micro/nanofiber meshes with 2 and 3 w v^{-1}% were fabricated by electrospinning of the pulp in an ionic liquid, 1-butyl-3-methylimidazolium chloride, and subsequently washed in water for 72 h. Ibuprofen (IBU), with an efficiency of 6%, were deposited on the fiber surface or trapped in the web porous areas by immersing the meshes in the IBU solution. During the fabrication process of the low concentration mesh (2 w v^{-1}%), the ionic liquid could not be washed off rapidly, and the fibers collected on the water surface were adhered together and created fusing areas. However, in the meshes with higher concertation of cellulose (3 w v^{-1}%), most fusing areas were disappeared. Furthermore, the higher concentration led to nano-scale fibers with a diameter of 1 µm or less, and the microscale fibers with a diameter of around 20 µm.

The IBU loading process did not influence the morphology of the cellulose fibers significantly. The frictional roughness, as an indication for skin irritation, was not significantly different between loaded and nonloaded nonwovens. Cell cytotoxicity assay performed on the nonwoven textiles showed that the normalized cells viability was more than 80%. The in vitro release studies revealed that 80% of IBU was released within 250 min from both 2% and 3% cellulose concentration meshes. In both meshes, the initial fast release within 100 min was attributed to the adsorbed surface of the fiber and fused fiber areas. The release kinetics based on Korsmeyer-Peppas was performed, and loaded nonwovens of the 2% and 3% showed typical Fickian diffusion mechanism ($Q_{2\%} = 8.35t^{0.42}$ ($R^2 = 0.9388$) and $Q_{3\%} = 18.53t^{0.26}$ ($R^2 = 0.9908$)).[317]

Adepu et al. produced a mesh for transdermal drug release to prevent undesirable toxic burst release of diclofenac sodium from encapsulated micropatterned CA electrospun nanofibers. The micropatterning via nylon meshes with 50 and 100 µm size openings produced a hydrophobic surface which assisted in controlling the initial burst release of the hydrophilic NSAID drug. The zero-order release profile changed from 30 min for nonpatterned mat to 12 h for the micropatterned mat.[262] This study suggests that fabrication of multilayered hydrophobic mats using different spinning methods would provide the opportunity to obtain a zero-order profile for an extended period.

In another example for the treatment of obesity, PVA fibers were fabricated and impregnated with curcumin encapsulated gelatin/albumin nanoparticles. The curcumin-loaded fibers form a fibrous transdermal drug delivery system for reducing the volume of subcutaneous adipose tissue. The fibers were optimized in terms of fiber dimension and porosity to achieve minimal drug diffusion time from the nanofiber matrix to the surface and to reach the maximum uniformity of the structure to increase the reproducibility of the drug release (Figure 8D-I).

Curcumin release profile was investigated in phosphate-buffered saline (PBS) and NaCl solution to simulate skin sweating in the existence of a transdermal mesh, where a burst release profile was observed in both solutions. NaCl solution reached a higher maximum release percent, more than 80% in less than 150 min, due to higher solubility of PVA and gelatin in water (Figure 8D-II). Whereas ex vivo transdermal test in a diffusion cell system using rat abdomen skin sample displayed a different profile with a delay in release rate in which the drug release reached 50% after 20 h.

The fast drug release was explained by the fact that the targeted tissue was below the skin and that the hydrophobic nature of the drug avoided quick evacuation of adipose tissue into the bloodstream. In vivo animal tests were conducted on the rats with high-calorie diets, and the results were analyzed by magnetic resonance imaging scans (MRI) and blood tests of leptin, triglyceride, and cholesterol. The results indicated that the volume percentage of adipose tissue in the treated group decreased significantly (4–7%), compared to the obese animals (Figure 8D-III).[318]

In between all the techniques used for fabrication of the drug-eluting transdermal textiles, electrospinning is the most studied one since it is a simple and cost-effective method. Moreover, unique characteristics including a large surface area to volume ratio, ultrafine fibrous structure, and high porosity with pore sizes ranging from submicron to nanometer make the electrospun nonwoven a suitable carrier for delivering various bioactive agents. An overview of drug-eluting medical textiles with their corresponding fiber spinning methods, drug impregnation techniques, release profiles, and kinetics are provided in Table 2.

7. Discussion

In the previous sections, fiber fabrication processes, drug loading methods, release mechanisms, and kinetics were reviewed. Drug-eluting fibers obtained from various raw materials vary extensively in terms of their chemistry and therefore performance characteristics. Moreover, various fabrication methods, such as melt- or wet-spinning, can be used both in the laboratory or industrial scales. The fabrication method depends on not only the raw material and the final application, but also dimension and shape of the fibers, biocompatibility of the solvent, and the processing parameters.[325,326] Woven and nonwoven structures from a broad range of natural to synthetic polymers or a combination

of them have been used in various biomedical applications, such as wound care, tissue engineering, and regenerative medicine, due to features such as a high surface area to volume ratio, porous structure, and surface modification and functionalization.

Bioactive agents could also be loaded into fibers both in pre- and post-fabrication stages. However, loading methods should be selected based on the parameters such as bioactive agent chemistry, optimal release profile, technical complexity of the spinning process, and the final application to avoid undesired results including low drug efficiency, degradation of the bioactive agents, poor mechanical properties, drug burst effect, and toxicity.[99] Mathematical models proposed to describe, quantify, and predict the kinetics of drug release can help to portrait a better picture of the drug release profiles; however, it should be realized that most models have been investigated based on laboratory-driven data with limitations compared to real conditions. Therefore, there is a demand to overcome the simplifications of these models by verifying and improving them with drug release data obtained from fibrous constructs in real applications.[42]

Recently, scientists have produced functional fibrous structures with the possibility of sensing the physiological data of the tissue and the ability to control drug delivery profiles.[327,328] Nanoscale sensors can be embedded into the medical textiles to enable a programmable responsive drug delivery system to tune the release profile of the bioactive agent.[132] The drug release can be triggered by environmental stimuli, such as pH,[329,330] temperature,[331] and chemical reactions or external stimuli, such as the magnetic field,[332] electric field,[333] and light.[334] For example, various metals including gold, silver, magnesium, and zinc can be patterned with low-temperature radiofrequency sputtering on the nanofibrous meshes to apply thermal stimulation to elute antibiotics when needed.

The stimulation can be manipulated via wires or wireless devices, such as smartphones. The use of smart textiles has been mainly investigated for wound dressing applications where integrated sensors could provide information on the healing status and the wound environment concerning its pH, bacterial level, tissue oxygenation, and inflammation.[335] The need for devices that can provide diagnostic information of the wound status and combat the infection is growing. However, improving sensor incorporation onto the fibrous network, stable sensors, and reliable networks for data management are required.[335]

The majority of studies reviewed in this article involve in vitro investigations of the drug-loaded fibers using different kinds of kinetic models. However, drug release and kinetics studies in vivo and in a "physiologically relevant" environment are very essential to move forward towards clinical studies and commercialization of the fibrous drug delivery systems.

Designing proper methods to fabricate drug-eluting textiles requires not only a sound understanding of the fabrication and loading techniques but also the theoretical perception of human physiological systems and their biological mechanisms. Engineering databases and the mathematical stimulations could be evolved for advanced computer-aided textile design by considering different physiological processes and the physicochemical functions of the textiles.[336] This can lead to achieving technical solutions with timely and cost-effective designs.

Finally, it should be noted that despite all the progress in the field of drug-eluting fibrous systems, there are still some limitations that should be addressed. For example, initial burst release of the drugs from fibers or aggregation of drug molecules on the surface of fibers can lead to undesired results. Using smart medical textiles and triggered drug-release systems could be applied to overcome some of the shortcomings of the current fibrous drug delivery systems. Lastly, due to the interdisciplinary nature of this field, fabrication of a functional drug-eluting fibrous system with a desired release profile requires the joint efforts of experts from different disciplines such as chemistry, biology, and engineering.

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Conflict of Interest

The authors declare no conflict of interest.

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